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- A Study of Methodologies

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ECONOMIC EVALUATIONS IN INTERNATIONAL HEALTH TECHNOLOGY ASSESSMENTS - A Study of Methodologies

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- A Study of Methodologies

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Foreword by DACEHTA

This methodological project is a review of a sample of economic evaluations carried out in international health technology assessment (HTA) reports. The report consists of tree major parts: 1) the development of a checklist by which to assess the state of the art of the economic evaluations in the international HTA reports, 2) the reporting of the results of the review of HTA economic evaluations, and 3) a review of economic evaluations in general published in scientific journals. The latter served two purposes: firstly as input into the development of the checklist, and secondly as a point of reference by which to compare the HTA economic evaluations.

The purpose of the report is to provide a general overview of the methods that have been applied in economic evaluation in HTA. This may provide helpful guidance to those who carry out economic evaluation in HTA. The report furthers an understanding of the methodological possibilities and limitations of economic evaluation as an integral part of HTA. It may hopefully help users of economic evaluations in HTA to critically appraise the methods as an important element of the interpretation of the results.

The report is a result of a project that was partly financed by funds granted by the Centre for Evaluation and Health Technology Assessment (DACEHTA) in 1999. The fund was given to Centre for Applied Health Services Research and Technology Assessment (CAST) at the University of Southern Denmark. Researchers from CAST and the Institute of Public Health, University of Southern Denmark, carried out the project.

The report is published in DACEHTA's series "Danish Health Technology Assessment". A report undergoes an editorial process and external peer-review by two relevant experts before publication in the series.

DACEHTA finds that the report is an important contribution to the development of the methods applied in health technology assessment.

Danish Centre for Evaluation and Health Technology Assessment
December 2003

Finn Børlum Kristensen
Director

Preface

This project is a methodology study funded by the Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) and Centre for Applied Health Services Research and Technology Assessment (CAST). A research team at CAST and the Health Economics Research Unit at the Institute of Public Health (IST), University of Southern Denmark carried out the work.

Rikke Juul Larsen (RJL) was the project leader. Jan Sørensen (JS) and Peter Bo Poulsen (PBP) were advisors for the whole review and analysis process. JS, PBP and RJL designed the study, and RJL constructed the checklist by which the HTA reports were reviewed. Mikael Asmussen (MA) and Torsten Christensen (TC) and RJL made up the review team. The work associated with the analysis of the results and the writing of the report was divided among the researchers, such that PBP is responsible for the review of economic evaluations in general in chapter 3, MA and TC are responsible for the review of sensitivity analysis, and Jens Olsen (JEO) is responsible for the reviews of costing and presentation of results. RJL is responsible for the description of methodology in chapter 2 and the reviews of study frame, study design, health outcomes, discounting and discussion of results and methodology.

RJL is the main author of this report, as she worked on the report during all its phases and is responsible for the technical aspects of the report. The rest of the authors appear in alphabetical order in the author list.

Thanks are due to our colleagues at CAST and IST for discussing our endeavors at two seminars and in particular Richard Brooks and Hindrik Vondeling for their detailed comments on the developed checklist and overall results. We also wish to thank Mike Drummond and Jakob Kjellberg for their peer review comments on an earlier version of this report, and Claire Gudex for eliminating traces of Danish grammar and spelling. The funding from DACEHTA (J.nr. 262-125-1999) is gratefully acknowledged.

The project group

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Executive summary

Background

Health technology assessment has received increasing attention in Denmark and elsewhere in the past 20 years as an instrument to support decision-making in health care policy and planning. An important component of health technology assessment is economic evaluation. However, there is limited knowledge as to what characterizes an economic evaluation in a health technology assessment, and as to how the health economic aspects are appraised within health technology assessment. The present study elaborates on this subject and focuses on the issue of *economic evaluation conducted as part of broader health technology assessment (HTA).*

Purpose

The aim of the study was to assess the state of the art of economic evaluation carried out as part of health technology assessments. In order to assess the HTAs, a checklist was developed and applied in a *literature review* of economic evaluations specifically carried out as part of HTA.

It was expected that the economic evaluations conducted under HTAs would not be as well developed as those used in economic evaluations in general and those recommended in guidelines. This was based on the presumptions that 1) the economic evaluation as part of a HTA is often only a small component in a comprehensive investigation of clinical and organizational problems, and 2) in a specific decision-making context, the economic evaluation may not carry much weight compared to, for example, budget analysis and the analysis of running costs. In order to test this hypothesis, the standard of economic evaluation in HTA was compared to that of economic evaluations carried out in general (that is, not specifically as part of health technology assessment) and to recommendations in guidelines for economic evaluation.

The study was a methodology study, focusing on the methods used in the reviewed health technology assessments rather than on the actual results of these assessments. The aim was to provide a general overview of the methods that have been applied in economic evaluation in health technology assessment. This should be useful for both "doers" and "users" of economic evaluations in HTA.

Methods

In order to construct a checklist to be used in the review of economic evaluations in HTA, the literature was first surveyed to find reviews (and checklists) that had already been conducted on the practice and quality of economic evaluations carried out in the health care field. The checklist for the present study was then constructed on the basis of these previous experiences. General checklists or guidelines (not applied to a specific literature review) and articles/books discussing methodological standards were also used in the development of the checklist. The Table below presents the topics that were included in the HTA checklist.

Main theme	Selected topics	Main theme	Selected topics
Identification (3 questions)	• HTA agency • Year of publication • Title	**Adjustment of differential timing** (4 questions)	• Time horizon • Discounting • Discount rate
Study frame (7 questions)	• HTA parameters (economic, clinical, patient, organizational) included • Type of health care intervention • Type of health technology • Purpose of study • Type of economic evaluation • Perspective of analysis • Comparators	**Presentation of results** (3 questions)	• Presentation of outcomes/ratios • Dominance/non-dominance • Incremental analysis
Study design (5 questions)	• Timing of economic evaluation in relation to clinical evidence • Sources of clinical evidence • Sample size • Modeling	**Handling of uncertainty** (4 questions)	• Areas of sensitivity analysis • Types of sensitivity analysis • Statistical analysis
Costs (19 questions)	• Identification of costs • Measurement of costs • Valuation of costs	**Discussion** (5 questions)	• Discussion of study results • Discussion of methodology • Comparison with other studies • Equity considerations • Representativeness
Health outcomes (14 questions)	• The health outcome in CEA • The health outcome in CUA • Methods of obtaining QALY scores • CBA methods	**General impression** (2 questions)	• Impression of the study • Reporting of the study

In order to identify HTA reports with an economic content, the websites of national agencies of health technology assessment were searched for relevant reports. A written request for further information was sent to selected HTA agencies. The criteria for inclusion of a HTA report in the review were: 1) publication by a national agency of health technology assessment that is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), 2) a HTA report written in English, Danish, Swedish or Norwegian, 3) a report including an economic evaluation (i.e. cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis), a cost-consequence analysis or a cost-analysis, and 4) an economic evaluation as a primary study, rather than, for example, a literature review.

Of 215 abstracts that were read, 91 (42%) did not have any economic content. Forty were classified as reviews of previous economic evaluations, and 17 were classified as economic analyses outside the remit of the present review (cost-of-illness studies, budget analysis etc.). The remaining 67 reports (31%) included an economic evaluation, a cost analysis or a cost-outcome description, and were therefore included in the review of economic evaluations carried out as part of health technology assessments.

Three economists individually reviewed each of the 67 HTA reports. Each economic evaluation was reviewed with the help of the specially developed checklist.

The reviewers discussed their ratings at regular meetings. The goal was to reach consensus with regard to each point in the checklist.

The data were analyzed using frequency tables, and cross-tabulations were made in order to investigate possible relations that might be relevant in describing the state of the art of economic evaluations as a distinct element in a health technology assessment.

It was also decided to conduct a literature review of the methods used in *economic evaluations in general* in order to establish a point of reference when evaluating the state of the art of *economic evaluations carried out as part of health technology assessments*. Reviews of economic evaluations in general were identified through a systematic search carried out in Medline, Embase, Cinahl and HealthStar. These articles in turn revealed further articles. A total of 40 reviews of economic evaluations of health technologies were identified, in which a checklist and an assessment of the methodological standard were included.

Results

With respect to *study frame,* the health technology assessments typically included two parameters (clinical and economic issues), the technology assessed was mostly a treatment and the intervention a procedure. The usual approach was a cost-effectiveness analysis from the perspective of the health system. Most of the economic evaluations were carried out retrospectively using secondary data in the form of a literature review or a meta-analysis. A majority of the economic evaluations were *designed* as models, in which the clinical data and cost data were assembled in a decision analytical framework.

A little more than one-third of the HTA economic evaluations used original data in the *measurement of resource use*, while another third used data from previously published studies. The identification and measurement of *costs* within the health care sector were often limited to the hospital sector (67% and 66% of the HTAs identified inpatient and outpatient costs, respectively) and used micro costing, patient-specific costing or case costing, implying a fairly detailed measurement. A patient questionnaire was the primary source of data on costs to the patients and their families. The reviewers judged that in half of the economic evaluations the choice of costs was appropriate in relation to the study perspective, whereas this was unclear in 48% of the evaluations reviewed. In two cases the choice of costs was judged to be inappropriate. Costs were generally valued by average costs or charges/rates, but in 22% of the HTA economic evaluations, it was not explicitly stated how the valuation was achieved.

The *health outcomes* used in the economic evaluations most often involved intermediate measures of effectiveness (34%, 23 HTAs), as opposed to 21% HTA economic evaluations using final measures of effectiveness, 16% using a QALY measure and 3% using benefit assessment. Seventeen HTAs did not use any measure of effectiveness as they were designed as cost analyses/cost minimization analyses (with no statement of the measure of effectiveness).

Practice regarding *discounting* of future costs and health outcomes varied. Most HTA economic evaluations stated the time horizon of the evaluation, but the majority did not discount the data (this was irrelevant for some HTAs where the time frame was less than one year). When considering the *presentation of results* in the health technology assessments, there was general adherence to guideline recom-

mendations, although a discussion of dominance/non-dominance and incremental analysis was absent in one-third of the HTAs. In 81% of the health technology assessments, uncertainty was handled by either *sensitivity analysis* and/or statistical analysis. The sensitivity analysis was most often a simple one-way analysis to test the variability in the data.

Finally, in regard to the *discussion of results and methodology*, all HTA economic evaluations included a discussion of the results, and three-quarters of them also included a discussion of the applied methodology. The representativeness of the results to routine practice was discussed in only 43% of the health technology assessments.

Conclusion

The state of the art of economic evaluations carried out as part of health technology assessments do not differ remarkably from that of economic evaluations in general. A notable exception is in the design, where the majority of the HTAs completed an economic evaluation retrospectively using secondary data in the form of a literature review or a meta-analysis. These data were often put together in a decision analytical model. This picture is not seen to this extent in economic evaluation in general, and is probably due to the nature of a health technology assessment as a synthesis of clinical and other evidence gathered from a systematic literature review.

The hypothesis that economic evaluations carried out as part of health technology assessments are not as well developed as economic evaluations in general can therefore be discarded. The use of cost-utility analyses was actually more widespread in the health technology assessments than in general economic evaluations studies, and there were also two cases where cost-benefit analysis was used. This indicates the application of advanced methods of economic evaluation in health technology assessment. With respect to the identification of resource use, the sample of economic evaluations that were conducted as part of HTAs more often identified the categories of patient and time costs than did the sample of economic evaluations in general. Half of the health technology assessments had a serious flaw, however, in that the perspective of the economic evaluation was not clearly stated.

1 Introduction

1.1 Background

Health technology assessment (HTA) has been described as "a systematic and comprehensive policy-oriented assessment of short- and long-term consequences of the use of health technology" (US Congress, 1976). As such, it has received increasing attention in Denmark and elsewhere over the past 20 years as an instrument to support decision-making in health care policy and planning. In line with this, more resources are being devoted to allow new studies in the field of HTA. Due to increasing restraints on the resources available to the health care sector, the economic component of HTAs has received additional attention, as documented earlier in an international comparison of HTAs (Poulsen & Hørder, 1998).

There is limited knowledge of what characterizes an economic analysis in a health technology assessment, and of how the health economic aspects are appraised in health technology assessments. Furthermore, the methodologies used in HTA economic analysis appear to be different to those used in traditional economic analysis (Liberati et al., 1997). Poulsen & Hørder (1998) evaluated 124 international health technology assessments in terms of the components that were included and found great variation in the health economic approach used. As their study did not aim at a thorough evaluation of the specific health economic components, however, the present study was undertaken, with a focus on *economic evaluations conducted as part of broader health technology assessments*.

1.2 Purpose of the study

The aim of this project was to assess the state of the art of economic evaluations carried out as part of health technology assessments. A checklist for assessing HTAs was developed and applied in a review of economic evaluations specifically carried out as part of health technology assessments.

It was expected that the economic evaluations conducted under HTAs would not be as well developed as those used in economic evaluations in general and those recommended in guidelines (i.e. they would not often apply technically advanced analyses such as cost-benefit and cost-utility analysis, discounting and sensitivity analysis). This was based on the presumptions that 1) an economic evaluation as part of a HTA is often only a small component in a comprehensive investigation of clinical and organizational problems, and 2) in a specific decision-making context, an economic evaluation may not carry much weight compared to, for example, budget analysis and an analysis of running costs. In order to test this hypothesis, the standard of economic evaluation in HTA was compared to that of economic evaluations carried out in general (that is, not specifically as part of health technology assessment) and to recommendations in guidelines for economic evaluation.

The project was a methodology study, focusing on the methods used in the reviewed health technology assessments rather than on the actual results of these assessments. The aim was to provide a general overview of the methods that have been applied in economic evaluation in health technology assessment. This should be useful for both "appliers" and "users" of economic evaluations in HTA. It is assumed that the target audience possesses a basic knowledge of economic concepts and definitions in general, and of health economic evaluation in particular.

1.3 Outline of the report

Chapter 2
Describes the methodology used to assess the economic evaluations. This covers the development of a checklist of main issues, the methodology used to review the economic evaluations conducted as part of health technology assessments, and the methodology of the general economic evaluation literature review. The principles of economic evaluation are also briefly described so as to establish and define the components of the checklist.

Chapter 3
Presents the results of a review of the methods used in economic evaluations in general, according to study frame and design, methodology used for costing and health outcomes, the use of discounting, presentation of results and the use of sensitivity analysis. The results in this chapter are intended as a standard of reference for the review of HTA economic evaluations.

Chapter 4
Provides a review of the state of the art of economic evaluation carried out as part of health technology assessments. The findings are presented with respect to study frame and design, methodology used for costing and health outcomes, the use of discounting, presentation of results, and the use of sensitivity analysis and discussion of results.

The results of the HTA and general reviews are compared and discussed in **Chapter 5**, and it is examined whether there exist certain patterns in the methods used in health economic evaluations. Comparisons are also made with the formal guidelines that exist for economic evaluation.

It is expected that the experienced health economist will be more interested in section 2.1-2.2 and Chapter 4, which describe the methodology and results of the HTA economic evaluation review, respectively. The less experienced reader might also benefit from reading section 2.3-2.4 (background and definitions of the points in the checklist) and Chapter 3 (results of the general literature review).

2 Methods

This chapter describes the methods used to develop the checklist, the methodology of the health technology assessment literature review, the methodology used to review health economic evaluations in general, and the main components of an economic evaluation (and hence of the checklist).

2.1 Development of a checklist

Before a literature review of economic evaluations in HTA reports can be conducted, a specific checklist has to be designed to ensure that the review will be complete and systematic. This checklist comprises a list of questions regarding the state of the art of economic evaluations carried out as part of health technology assessments. The methods used to develop the checklist are described in the section below, while a more detailed description of the background and definitions of the checklist components are provided in section 2.4.

2.1.1 Literature review of published checklists

In order to construct a checklist to be used in the literature review of economic evaluations in HTA, a survey of the literature presenting checklists and reviews on the practice and quality of economic evaluations conducted in the health care area was carried out. Each article was studied with respect to the checklist components and/or review issues included, and then the various checklists were compared. A judgment was made as to which components should be included in the checklist for the present review of economic evaluations in HTA, on the basis of these experiences from previous checklists and literature reviews. General checklists or guidelines (not applied to a specific literature review) and articles/books discussing methodological standards in economic evaluation were also used in the development of the checklist, e.g. Drummond et al. (1997a) and CCOHTA (1997).

In comparing the checklists, their most likely origin was searched for. It appeared that most of the checklists were connected in some way to the 10-point checklist published by Drummond et al. (1997a). This checklist is an adaptation of the checklist that Williams (1974) presented in his article about the cost-benefit approach, which was the first checklist constructed to assess the practice of economic evaluations. In the article by Drummond et al. (1997a), these points were combined and elaborated and some new points were added (Maynard, 1997).

Few of the checklist reviews used the Drummond et al. checklist in full; one of those that did is the literature review performed by Lee & Sanchez (1991). Most of the literature reviews had modified the checklist in some way, either by formulating minimum standards (such as Udvarhelyi et al., 1992), or by adding items to the checklist. Some authors omitted the epidemiological/clinical elements in the Drummond et al. checklist (e.g. Bradley et al., 1995), while others had a special interest in one of the components of the Drummond et al. checklist (e.g. Gerard (1992) focused on the cost-utility approach to economic evaluation and therefore included extra items that applied to this specific area).

Inspired by the checklist published by Drummond et al. (1997a), all the checklists found were described and compared with respect to five main headings: *study frame* (study question, alternatives, sample selection, study model), *costs* (identification, measurement, valuation, adjustment for differential timing), *consequences* (identification, measurement, valuation, adjustment for differential timing), *analy-*

sis (incremental analysis, statistical analysis, sensitivity analysis) and finally *presentation and discussion* (assumptions and limitations of the study, external validity, and other issues of concern to users). Note that this was only the framework for comparison and analysis, and was not the final checklist for assessing economic evaluations undertaken as part of HTAs.

2.1.2 Comparison of checklists

A checklist consists of a number of checkpoints related to the main themes (e.g. design, costs and consequences) that the list covers. As more than one hundred checkpoints were identified in a comparison of various checklists, it was useful to divide these according to the subheadings presented in the previous section. On the basis of simple quantitative criteria, the first draft of a checklist was produced as a consensus finding from the different checklists reviewed. This first checklist model, shown in Box 2.1, included the checkpoints that were recommended in 75% or more of the reviewed checklists.

Box 2.1 Checklist 1

1. Was the perspective of the analysis stated?
2. Was a comprehensive description of the alternatives given?
3. Were all the important and relevant consequences for each alternative identified?
4. Were consequences, which occur in the future, discounted to their present value?
5. Were all the important and relevant costs for each alternative identified?
6. Were costs, which occur in the future, discounted to their present value?
7. Was an incremental analysis of costs and consequences of alternatives performed?
8. Was sensitivity analysis performed?

As can be seen from Box 2.1, more than 75% of the articles presenting checklists or reviews agreed that a perspective for the analysis should be stated. Similarly, a comprehensive description of alternatives was recommended by 75% of the studies. Very few articles, however, included checkpoints relating to sample selection and study design, which is troublesome, as these are important aspects of an economic evaluation and the recommendations that are drawn from it. As Salkeld et al. (1995) noted: "Economic evaluation relies on the results of epidemiological and clinical studies to establish the effectiveness of an intervention. … A study based on poor evidence of effectiveness has the potential to mislead both clinical and resource allocation decision-making." It is therefore imperative that economic evaluations consider, state and discuss the chosen study design, in order to make this explicit.

The identification of relevant costs and consequences and their adjustment for differential timing were considered important by the majority of the reviewed studies, although few included the actual measurement and valuation of these costs and consequences in their reviews.

The principle of an incremental analysis was recommended by 75% of the checklist studies, while almost 90% considered sensitivity analysis to be an important element. Only one of the checkpoints relating to presentation and discussion of the economic evaluation results received general agreement - that the conclusions of the analysis should be based on an overall index or ratio of costs to consequences. It is worrying that so few studies attach importance to the presentation and discussion of the results, which would normally include a discussion of the assumptions and limitations of the study, the external validity (and thereby the generalizability)

of the study, the relevance of the study to policy, and other issues of concern to potential users, e.g. the comparison of results with those of other studies, and ethical issues. These are very important issues that should be discussed in every study.

The checklist presented in Box 2.1 thus includes some key issues in economic evaluation, but is neither exhaustive nor detailed enough when compared to, for example, guidelines for economic evaluation. The checklist represents a minimum standard for performing economic evaluation and is very similar to the checklist developed by Udvarhelyi et al. (1992) for this particular purpose. To obtain a more comprehensive checklist, other issues need to be included e.g. issues of study design, sample selection, measurement and valuation of costs and consequences, and a general discussion of the study. A second checklist model, which is shown in Box 2.2, was therefore created from the checkpoints that were recommended in 50% or more of the reviewed checklists.

Box 2.2 Checklist 2
Items 1-8 from Checklist 1, plus
9. Were all relevant alternatives included?
10. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences?

It can be seen that Checklist 1 was enlarged by only two checkpoints, and some important issues were still missing. In order to construct a sufficiently complete and detailed checklist for economic evaluations undertaken as part of HTAs, it was therefore necessary to go beyond a comparison of previously published checklists and to draw on knowledge and expertise in the field of economic evaluation.

2.1.3 The final checklist

The third, and final, checklist model was created by expanding Checklist 2 to include other relevant checkpoints that, despite not being recommended by the majority of reviewed checklist studies, were considered to be important by the authors of the present report. This final checklist also had a higher level of detail. As the aim of the present study was not a normative assessment of the *quality* of economic evaluations, but rather an assessment of the state of the art of economic evaluations in HTAs, it was necessary to include in the checklist some very specific questions relating to the practice of economic evaluation. Furthermore, some topics specifically related to HTA needed to be included. The result was a comprehensive checklist of questions that consisted of ten main themes, each covering a number of topics. The ten themes and their main topics are illustrated in Table 2.1. The checklist as a whole is presented in appendix A.

Table 2.1
The ten themes and main topics of the final checklist for reviewing economic evaluations undertaken as part of health technology assessments

Main theme	Selected topics	Main theme	Selected topics
Identification (3 questions)	• HTA agency • Year of publication • Title	**Adjustment of differential timing** (4 questions)	• Time horizon • Discounting • Discount rate
Study frame (7 questions)	• HTA parameters (economic, clinical, patient, organizational) included • Type of health care intervention • Type of health technology • Purpose of study • Type of economic evaluation • Perspective of analysis • Comparators	**Presentation of results** (3 questions)	• Presentation of outcomes/ratios • Dominance/non-dominance • Incremental analysis
Study design (5 questions)	• Timing of economic evaluation in relation to clinical evidence • Sources of clinical evidence • Sample size • Modeling	**Handling of uncertainty** (4 questions)	• Areas of sensitivity analysis • Types of sensitivity analysis • Statistical analysis
Costs (19 questions)	• Identification of costs • Measurement of costs • Valuation of costs	**Discussion** (5 questions)	• Discussion of study results • Discussion of methodology • Comparison with other studies • Equity considerations • Representativeness
Health outcomes (14 questions)	• Health outcome in CEA • Health outcome in CUA • Methods of obtaining QALY scores • CBA methods	**General impression** (2 questions)	• Impression of the study • Reporting of the study

Some of the issues raised relating to the application of economic evaluation naturally have a high level of agreement among economists, while others have only a low level of agreement. The issues with low and high agreement are illustrated in Table 2.2.

Table 2.2
Levels of agreement in the practice of economic evaluation

High level of agreement	Low level of agreement
• Economic evaluation terminology (i.e. CEA, CUA, CBA) • Superiority of marginal costing • Importance of considering alternatives • Importance of analytical viewpoint and the need to consider the societal viewpoint • Discounting • Importance of performing sensitivity analysis	• Inclusion of indirect costs and benefits • Inclusion of health care costs in added years of life • Choice of discount rate for health benefits • Method of measuring health state utilities • Incorporation of equity considerations in economic evaluations • Inclusion of intersectoral consequences of health care programs

Source: Drummond et al. (1993) and Gerard (1992)

Even though the lists in Table 2.2 were published 10 years ago, they appear still to apply today, as there is no consensus as yet on the issues with low agreement. It could be argued, however, that there is no general agreement that a societal point of view should be applied in an economic evaluation – this is otherwise included in the list of issues with a high level of agreement. Gerard (1992) stated that this was not always the case. All the items in Table 2.2, except the inclusion of health care costs in added years of life and the inclusion of intersectoral consequences of health care programs, are included in the checklist developed for the present study.

2.2 Methodology of the HTA literature review

2.2.1 Selection of reports

Inclusion and exclusion criteria

There were certain criteria that HTA reports had to meet to be included in the literature review. First, they should be published by a *national agency* of health technology assessment that is a member of the International Network of Agencies for Health Technology Assessment (INAHTA). Second, the HTA reports should be written in *English, Danish, Swedish or Norwegian*. Third, the reports had to include an *economic evaluation* (see below), where a health technology was compared to at least one other health technology, i.e. where a comparative economic analysis (CMA, CEA, CUA, CBA) was performed, or both costs and consequences were included in a cost-outcome analysis, or costs were included in a comparative cost-analysis (CA). Fourth, the economic evaluation in the reports had to be conducted as a *primary study* rather than, for example, a literature review.

Different types of economic analysis exist, as shown in Table 2.3. They can be categorized with respect to two features of economic analysis. First by whether they include both costs and consequences or only one of the above, and second by whether a comparative analysis between at least two health technologies is employed or not. The gray areas in Table 2.3 indicate the types of economic analyses that are *not* included in the present literature review due to the inclusion criteria mentioned above. Besides full economic evaluations, cost analyses were included as they still incorporate a comparison of alternatives even though the consequences are not included. It can often be quite difficult to distinguish between a cost analysis and a cost-minimization analysis, which is a further argument for including the cost analyses. Cost-outcome analyses were also included, as they involve an assessment of both costs and consequences, although not a comparison with alternative technologies. In the rest of this report, all the different types of analyses that are included in the literature review are included under the term ‘economic evaluation’.

Table 2.3
Categorization of economic analyses

		Are both costs and consequences of the alternatives examined?		
		No		**Yes**
Is there a comparison of two or more alternatives?	**No**	Partial evaluation		Partial evaluation
		Examines only consequences	Examines only costs	Cost-outcome analysis
		Outcome description	Cost description - including cost-of-illness	
	Yes	Partial evaluation		Full economic evaluation
		Efficacy or effectiveness evaluation	Cost analysis (CA)	Cost-minimization analysis (CMA) Cost-effectiveness analysis (CEA) Cost-utility analysis (CUA) Cost-benefit analysis (CBA)

Source: Drummond et al. (1997a)

Studies comprising only outcome descriptions or cost descriptions (including cost-of-illness analyses), which were neither comparative nor included both costs and consequences, were excluded from the literature review. Effectiveness evaluations were also excluded, as they do not incorporate any consideration of costs, which are a main focus of an economic analysis. Further, it was decided to exclude analyses that focused on a single budget (budget analyses) or on the running costs of a hospital/department; these analyses were too narrow in their perspective and they often do not include a comparison of alternatives or incorporate the consequences. Finally, literature reviews of previously published economic evaluations presenting results in a specific area (secondary research) were excluded since the aim of the present study was a review of primary research only.

Study identification and selection

In order to identify HTA reports with an economic content, the websites of the national agencies of health technology assessment were searched. A list of the agencies included in the present review is provided in appendix B. Twenty *national HTA agencies* were identified; the rest of the INAHTA members were excluded since they are not national agencies, but either regional agencies or research institutions. The selected agencies were informed about the study in a letter, and were asked for information regarding their published reports, i.e. whether they had any reports containing an economic evaluation, and what language the reports were written in. Reports were thus identified through a combination of searching the websites of national agencies and a mail survey of the agencies.

A pilot study was performed with the purpose of examining whether HTA reports containing an economic evaluation could be identified on the basis of their abstracts only. Twenty-seven HTA reports were selected based on inspection of the abstracts. The reviewers in the pilot study (PBP and JS) individually performed the assessment and generally agreed upon the categorization of the abstracts. Therefore it was decided that it was not a problem to select HTAs for inclusion on the basis of abstracts only.

Abstracts of all the relevant reports written in English, Danish, Swedish or Norwegian were downloaded from the websites or ordered by mail. The last search of the websites was performed on March 1, 2000. One of the reviewers (RJL) read all the abstracts (215), and the reports that appeared to include an *economic evaluation* were selected. In uncertain cases, the full report was read to determine whether or not an economic evaluation had been included as part of the HTA. Following this selection procedure, 67 reports were found that incorporated an economic evaluation and therefore formed the basis for the review. The selection of reports is illustrated in Table 2.4. The first column lists the national agencies that were originally included in the study, as defined above. The second column indicates the number of reports published in English, Danish, Swedish or Norwegian. The third column shows the number of reports that incorporated an economic evaluation and were thus included in the final sample to be reviewed.

As shown in the second column of Table 2.4, 215 abstracts were read. Ninety-one of these did not have any economic content, which is almost half of the reports (42%). Of the remaining 124 reports, 40 were classified as reviews of previous economic evaluations, and 17 were classified as economic analyses excluded from this review (cost-of-illness, budget analysis etc.). The remaining 67 reports (31%) included an economic evaluation, a CA, or a cost-outcome description, and were therefore included in the review of economic evaluations carried out as part of health technology assessments. Appendix C contains a list of the HTAs included in the HTA economic evaluation review.

Table 2.4
Selection of reports

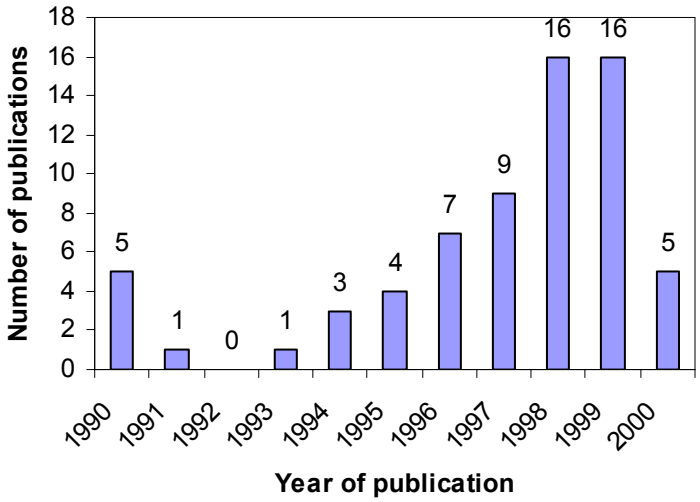
National agencies initially included in the review [1]	N° of reports that satisfied the language criteria	N° of reports that included an economic evaluation conducted as primary research
AETS	0	-
ANAES	0	-
AHRQ	23	1
ASERNIP-S	4	0
CCOHTA	37	19
CVZ	0	-
DIHTA	12	6
DIMDI	0	-
ETESA	0	-
FINOHTA	12	5
ICTAHC	1	1
INHEM	0	-
ITA	2	0
MSAC	10	2
NCCHTA	48	22
NZHTA	11	0
SBU	41	11
SMM	5	0
SFOSS/SWISS-TA	0	-
VATAP	9	0
TOTAL	**215**	**67**

1) The agencies are listed in appendix B with their full names

An investigation was made into the year in which the 67 HTA reports identified for review were published. Figure 2.1 shows that the reports were published between

1990 and 2000. The number of reports published in 2000 appears to be very low, but this is due to the cut-off date for inclusion of studies being 1st March 2000. If this result were linearly extrapolated to include the rest of the year, the result would be publication of 20 reports. It is clear that the majority of the included reports were published in the years 1996 to 2000. Although the reasons for this were not investigated, it is probably due to two contributory factors: there is an increasing number of HTAs being undertaken, and it is becoming more common to include an economic evaluation in health technology assessments.

Figure 2.1
Year of publication of 67 reviewed HTA reports



2.2.2 Review methodology

Reliability and validity of the review

Once the checklist had been constructed and the economic evaluations had been selected for review, the literature review could proceed. To test consistency between the reviewers, the checklist was initially piloted on 10 studies. This caused some adjustments to be made to the checklist. Furthermore, a set of instructions for use of the checklist was developed. These instructions contained detailed information about each checkpoint and a description of the possible issues. Important terms were also defined. These instructions served therefore as a "reference manual" for the reviewers and helped to produce consistency in the ratings. The instructions were based on the definitions provided in chapter 2.4.

In view of the controversies that exist over some of the issues relating to economic evaluation, total agreement between the reviewers could not be established on every checkpoint. It was therefore decided to hold regular consensus meetings, where the reviewers' scores on the checklist were compared. If there were any disagreements in the scoring, a consensus was reached through discussion. Senior health economists were consulted in the very few cases where consensus could not be reached.
Some problematic areas were identified, where the reviewers often disagreed. These areas were: 1) Measurement of resource use, 2) Valuation of costs, and 3) Discussion of the methodology and methodological limitations. The main reason for problems with the determination of measurement of resource use might be that the categories were not mutually exclusive, as a measurement of resource use can

be patient-specific and at the same time use a micro-costing approach. Furthermore, the different items of resource use were often measured in different ways, and it could be quite difficult to determine which was the primary resource unit. This latter explanation also applies to the valuation of costs. The third problematic area was the discussion of methodology and methodological limitations. It will always be very difficult to determine when exactly an issue has been discussed and when it has merely been mentioned, since this is a subjective matter. How many lines should be written before it can be called a discussion? This problem was more or less solved by deciding that as soon as the issue was mentioned, it was also discussed unless otherwise stated in the report (e.g. "this issue will not be discussed").

The review process

Three economists (RJL, TC, MA) individually reviewed each of the 67 HTA reports. Each economic evaluation was reviewed using the checklist constructed specifically for the present study. The checklist was very detailed, with 63 questions to be answered for each economic evaluation. The content of the checklist is discussed in section 2.4 and can be seen in appendix A.

Each reviewer read the economic evaluation and completed the checklist according to the accompanying instructions. The reviewers discussed their ratings at regular meetings, where the goal was to reach consensus with regard to each point in the checklist. A consensus checklist was therefore completed for each economic evaluation.

2.2.3 Data analysis

The data were analyzed using frequency tables (and other ways of showing the distribution of answers, e.g. diagrams). Cross-tabulations were performed in order to test possible relations that might be relevant in describing the state of the art of economic evaluation as a distinct element in health technology assessment.

2.3 Method used to investigate economic evaluation reviews in general

It was decided to conduct a literature review of the methods used in health economic evaluations in general (chapter 3) in order to be able to compare the results from the review of economic evaluations carried out as part of health technology assessments (chapter 4).

The literature reviews included in chapter 3 were identified through a systematic search carried out in Medline, Embase, Cinahl and HealthStar. The search identified 24 articles, of which 17 articles were discovered through Medline, four through Embase, one through Cinahl and two through HealthStar. A further 16 relevant articles were identified through the reference list of other literature reviews or were already known to the present authors. In total, 40 reviews of economic evaluations of health technologies that included a checklist and an assessment of the methodological standard were identified. Appendix D describes the search strategy and provides further details of the literature search.

Review articles exclusively presenting results on the cost-effectiveness of health technologies, e.g. the cost-effectiveness of health interventions in the area of Alzheimer's disease as in Ernst & Hay (1997), were excluded from the review, as they did not fulfill the criteria of being a literature review of the methods used in economic evaluations. Guidelines on the performance of economic evaluations (e.g. Drummond et al. (1997b), and articles only presenting checklists (e.g. Sacristan et

al., 1993), were also excluded, as they primarily described ideal behavior and not actual practice. Later in this report the results of the present study are compared, however, with the growing number of guidelines for economic evaluations that are published in Denmark, Canada and elsewhere.

As seen in Table 2.5, most of the 40 economic evaluation review studies (28; 70%) presented reviews of economic evaluations and the methods used.

Table 2.5
Literature reviews of economic evaluations in the health care area

	Focus				Journal		Specific area of review
	Economic Evaluation	Costs	Outcome[1]	Uncertainty	General journal[2]	Specialist medical journal	Medical specialty area of the Economic Evaluations
1 Adams et al. (1992)	X					X	General – Randomized Controlled Trials
2 Agro et al. (1997)				X	X		General
3 Allred et al. (1998)	X					X	Nursing literature
4 Amin et al. (1998)	X					X	Schizophrenia
5 Anell & Norinder (2000)			X		X		General (HEED database)
6 Blackmore & Magid (1997)	X					X	Radiology
7 Blackmore & Smith (1998)	X					X	Radiology
8 Bradley et al. (1995)	X					X	General
9 Briggs & Schulper (1995)				X	X		General
10 Briggs & Gray (1999)				X		X	General
11 Brown & Schulper (1999)			X		X		Cancer therapies – contingent valuation
12 Chang & Henry (1999)		X				X	Nursing, medical and health services lit.
13 Diener et al. (1998)			X		X		General, contingent valuation
14 Evers et al. (1997)	X				X		Mental health care interventions
15 Evers et al. (2000)	X					X	Stroke
16 Ferraz et al. (1997)	X					X	Rheumatology and related disciplines
17 Gambhir et al. (2000)	X					X	Nuclear medicine
18 Ganiats & Wong (1991)	X					X	General
19 Gerard (1992)	X				X		General – cost-utility analyses
20 Gerard et al. (1999)	X				X		General – cost-utility analyses
21 Gerard et al. (2000)	X				X		General – cost-utility analyses
22 Jacobs & Bachynsky (1996)		X			X		General – costing in the Canadian lit.
23 Jacobs & Fassbender (1998)		X			X		General – indirect costs

[1] The studies focusing on outcome considered health status measurement or contingent valuation methods.
[2] Health Economics, Health Policy, Pharmacoeconomics, International Journal of Technology Assessment in Health Care and Social Science and Medicine were considered as general journals in the field of economic evaluation.

24	Kristiansen & Poulsen (2000)	X					X	Telemedicine
25	Lee & Sanchez (1991)	X					X	Pharmacy literature
26	Maetzel et al. (1998)	X					X	Rheumatology and related disciplines
27	Morris et al. (1997)	X					X	Hypercholesterolaemia
28	Rothfuss et al. (1997)	X					X	Rheumatoid arthritis and osteoarthritis
29	Rutten-Van Mölken et al. (1992)	X				X		Asthma and COPD care
30	Saleh et al. (1999a)	X					X	Knee arthroplasty literature
31	Saleh et al. (1999b)	X					X	Hip arthroplasty literature
32	Salkeld et al. (1995)	X				X		General – but only Australia
33	Schrappe & Lauterbach (1998)	X					X	HIV
34	Sluthuus (2000)		X			-	-	General
35	Smith & Blackmore (1998)	X					X	Obstetrics and gynecology literature
36	Stone et al. (2000)		X			X		General – costs in cost-utility analyses
37	Taylor & Chrischilles (1997)	X					X	Endocrinology, diabetes mellitus, osteoporosis
38	Udvarhelyi et al. (1992)	X					X	General
39	Walker & Fox-Rushby (2000)	X				X		Communicable disease – developing countries
40	Weatherly et al. (1999)		X			-	-	General (NHS EED database)

The other reviews focused either on methods used to measure costs (6 literature reviews), different types of outcome measurement (3 literature reviews), or were even detailed reviews of how the issue of uncertainty was dealt with in published economic evaluations (3 literature reviews).

The 40 literature reviews presented and summarized in this section cover approximately 3,000 economic evaluations of different health care technologies. It is likely, however, that some of the economic evaluations are included more than once. It was not possible to control for this by just reading the review studies and a more detailed investigation of the economic evaluations included was impossible, as the individual studies reviewed were not always listed in the literature review studies. Although it is still high, the actual number of different economic evaluations covered is therefore somewhere less than 3000.

More than half of the literature reviews (22) reviewed economic evaluations that either were conducted within medical specialty areas such as rheumatology, radiology and telemedicine, or were restricted to economic evaluations that were published in specific journals, such as the nursing or pharmacy literature. For most of these studies, therefore, publication in specialist medical journals was more relevant than in general journals. Eighteen of the literature reviews could be regarded as general, although still with a focus on economic evaluations in the health care area. Four of these reviews were restricted to cost-utility analyses (Gerard, 1992; Gerard et al., 1999; Gerard et al., 2000; Stone et al., 2000). Some of the general review studies took the advantage of using existing literature databases of economic evaluations, such as the NHS Economic Evaluation Database. One of these studies was a review study by Weatherly et al. (1999), in which the objective was to identify characteristics of the costing methods that were used in health technology assessments. However, by choosing the NHS Economic Evaluation Database, these authors appear to define economic evaluation as being identical to health technology assessment. In reality, economic evaluation is frequently considered as a partial technology assessment (Poulsen & Hørder, 1998). It can therefore be con-

cluded that none of the literature reviews published so far have exclusively dealt with *economic evaluations conducted as part of broader health technology assessments*, which is the focus of the present study.

The results from the 40 literature reviews on economic evaluation are presented in Chapter 3. In order to compare these with the results reported in Chapter 4, they were structured according to the main points in the checklist developed for this study. These checkpoints were: *type of economic evaluation, perspective, alternatives chosen, study design, costing (identification, measurement and valuation), health outcomes, discounting, cost-effectiveness (CE-ratio, incremental analysis),* and *handling of uncertainty*. Results concerning the discussion of results and methodology in the particular study were not reviewed in chapter 3.

2.4 Background and definitions of the issues in the checklist

This section provides further details about the themes and topics that are included in the checklist for evaluating economic evaluations in HTAs. As such it include a definition of the different topics, and the diverse methods to be used in these. As a point of reference, the checklist itself is provided in appendix A.

The first questions in the checklist related to *identification* of each economic evaluation that was included in the literature review. These questions enquired about author, year of publication, title of the HTA report, title of sub-report or published article (if relevant), and name of the HTA agency that published the report. The reviewer's name (or 'consensus version') was also noted on each completed checklist.

2.4.1 Study frame

Some of the issues relating to study frame apply specifically to the economic evaluation, while others apply to health technology assessment (HTA) in general.

Topics specifically related to economic evaluation

The key issues that determine the frame of the economic evaluation are the purpose of the evaluation, the type of evaluation performed, the perspective of the analysis and the use of comparative analysis.

The *purpose* of the economic evaluation in a HTA must be explicitly stated, as this determines which type of economic evaluation should be used, as well as its perspective and relevant comparators.

The *types* of economic evaluations that were included in this review were cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-minimization analysis (CMA), cost-outcome descriptions[3] and cost analyses (CA)[4]. While the approach to cost measurement and valuation is identical in all these different types of economic analysis, a difference appears in the measurement and valuation of the health outcomes. For a more detailed description of the outcome measures, see section 2.4.4.

The *perspective* of an economic analysis can vary from that of society to that of the hospital department or the patient. The broadest is the societal perspective, in

[3] Also called 'cost-consequence descriptions'
[4] See section 2.2.1 for explanation of how these types of economic evaluation were chosen.

which all costs are considered, no matter to whom they accrue. In a public sector perspective, the costs borne by the health care sector and other sectors (most often the social sector) are included, whereas in a health care sector perspective only the costs to the health care sector (primary and secondary) are included. The perspective of a single hospital/hospital department can be applied, and of course a patient perspective will also be relevant at times, although seldom in a HTA. In countries where the health care system is financed through, for example, insurance, the perspective of the third party payer might also be of relevance; in this case the costs accruing to the payer are considered.

If an economic evaluation is used to prioritize between health technologies on a societal level, then a societal perspective must be applied; otherwise there is the risk that the prioritization will not be optimal. Both Danish and Canadian guidelines recommend that the societal perspective be applied (Alban et al., 1998; CCOHTA, 1997) . Other perspectives might be of relevance, depending on the decision-problem that the HTA is supposed to illuminate, and hence the decision-maker that the HTA is addressing. For a further discussion of the relationship between perspective and choice of cost components, see section 2.4.3.

A characteristic of an economic evaluation is that it is a *comparative analysis* – the health care technology of interest is compared to at least one other alternative health care technology. This alternative could be the intervention used before the new intervention was introduced, some gold standard, the 'do-nothing' alternative or the placebo alternative. The important issue here is that the comparator is relevant.

General HTA-related topics

A HTA includes *other parameters* besides the economic evaluation. HTA has been defined as "a systematic and comprehensive policy-oriented assessment of short- and long-term consequences of the use of health technology" (US Congress, 1976). In Denmark, four key themes have been developed to ensure that all relevant topics are considered when performing health technology assessment. These four themes are (DACEHTA, 2000a): *clinical parameters* including efficacy, safety, effectiveness, indications etc.; *patient-related parameters* including psychological factors, ethics, acceptability, satisfaction; *organizational parameters* including diffusion, centralization/decentralization, access, education/training; and *economic parameters* including economic evaluation, analysis of running costs, budget analysis, etc.

It is important that the HTA specifies the *type of health care intervention* under study; this can be treatment, diagnostics, screening, prevention or nursing care. *Treatment* is defined as an intervention where the aim is to improve or eliminate a diagnosed disease, while *diagnostics* is the examination of presumed ill persons, contrary to *screening*, which is an examination of presumed well persons. While screening is secondary prevention (asymptomatic individuals are examined), *prevention* can be primary (to reduce the number of new cases), secondary (to reduce the number of already established cases in the society) or tertiary (to stabilize or reduce the size of the handicap in connection with the disease). *Nursing care* can of course be part of the treatment (e.g. in postoperative surgical recovery), but can also be given where active treatment has been stopped (e.g. palliative care).

The *type of health care technology* can also take different forms, as it can be a drug, a device or a procedure. A *drug* is defined as a chemical or biological substance that is applied to, ingested by or injected into the relevant persons, whereas

devices are defined as any physical items (except drugs) that are used in health care (Banta & Luce, 1993). A *procedure* is defined as the process of the intervention, e.g. simultaneous or sequential kidney and pancreas transplantation. If a specific drug or a comparison of drugs is the primary aim of the economic analysis, then the technologies compared should be defined as drugs, and likewise for devices. If, on the other hand, devices or drugs enter into a procedure, but are only secondary in relation to the process, then the technology should be defined as a procedure. According to Banta & Luce (1993), a procedure is a combination of provider skills or abilities with drugs, devices or both, where the key to the procedure is the doctor's actions and not the drug and/or the device.

2.4.2 Study design

The study design defines how the economic evaluation is carried out with respect to prospective/retrospective data collection, sample size, source of clinical evidence and modeling. These are important – and sometimes overlooked – issues in economic evaluations, where the focus is often on costs and health outcomes, and the epidemiological foundations of the data are given low priority.

Firstly, it is important to know how and when an economic evaluation is linked to the collection of clinical data. If the economic evaluation is performed *retrospectively* in relation to the clinical data collection then the economic evaluation is conducted with previously collected clinical data from, for example, an earlier clinical trial, a literature review/meta-analysis or a database. If, on the other hand, the economic evaluation is conducted *prospectively* then the data on costs and consequences are collected at the same time and connected to the collection of clinical data. It is becoming increasingly common to conduct prospective studies, with the economic evaluation 'piggy-backed' onto a clinical trial (Drummond et al., 1997a). This method has the advantage that a *patient-specific link* appears between input (resource use), output (intervention) and outcome (e.g. effectiveness). This link is assumed in studies that are performed retrospectively.

The gathering of clinical/epidemiological evidence can be either primary or secondary. *Primary methods of data collection* indicate that primary data are collected in order to investigate the problem under study. Primary methods include the randomized controlled trial (RCT), observational studies, case-control trials, and other studies where the data are gathered first-hand. The *secondary methods of data collection* indicate data that have been collected previously in order to investigate a different problem to that currently under study. Secondary methods include literature reviews, which can be either systematic or unsystematic, and can include a pooling of results as in meta-analyses. A meta-analysis can furthermore include RCTs or non-RCTs. A meta-analysis is a process of combining study results in such a way as to be able to draw conclusions about therapeutic effectiveness. Other forms of secondary methods are expert panels, databases (e.g. a database of causes of death) and public files (e.g. administrative databases). Expert panels estimate the clinical effect of the health technology by means of personal opinion and expertise. Such panels should only be used when no other alternative for obtaining the relevant data is available (e.g. when the efficacy of a health technology is used to make inferences about the effectiveness of the health technology) or for quality assurance of the available data.

Economic evaluation is often a synthesis of information from several disciplines, such as epidemiology, clinical research and economics. A *model* is an excellent

way to combine this information; usually, a decision tree or a Markov model is applied in modeling studies.

There is no easy answer as to which sort of data should be used in an economic evaluation, and each method has its advantages and disadvantages. It is usually recommended to use effectiveness data rather than efficacy data, however, as the former better reflect normal clinical practice (Drummond et al., 1997b; Torrance et al., 1996). In summary, different approaches can be taken to the collection of clinical and cost data:

Prospective economic data collection alongside RCT has the advantage of high internal validity[5] and the formation of a patient-specific link between resource use, intervention and outcome. The disadvantage is that the results may not reflect normal clinical practice so well (low external validity) and therefore not be widely generalizable.

Retrospective data collection tends to produce more generalizable results as the data usually come from daily clinical practice. The disadvantage is the lack of proof that a difference in cost or effectiveness is actually caused by differences in the technologies compared.

Modeling is a broad synthesis of trial data and other evidence and is often used where the data require adjustment before they can be used in an economic evaluation. This is most often the case with efficacy data that do not reflect normal clinical practice, and RCT data that have a short time horizon (economic evaluations often seek to estimate lifetime costs and consequences). The disadvantage of modeling is that disparate information from perhaps very different populations are combined in a model without any evidence that this is a true reflection of the world.

The *sample size* needed to detect a minimally relevant significant difference is often not calculated in economic evaluations, or at least it is not apparent that such an exercise has been performed. This is a problem as the variation in resource use can be quite pronounced. If the sample size is calculated in relation to the relevant clinical differences between two health technologies, then this might not result in statistically significant differences in resource use or cost-effectiveness ratios. It is therefore necessary to calculate sample size on the basis of economic endpoints (Johnston et al. 1999). Studies were therefore examined to see whether the calculation of sample size had been explicitly considered.

2.4.3 Costs

The stage of costing is one of the most central and often most resource intensive activities when performing an economic evaluation. The basic (theoretical) cost concept is that of opportunity cost: the cost must express the benefit that could be obtained by the best alternative use of the resources.

A cost is characterized by the consumption of resources. The first step in the costing process is *identification* of the relevant resource use involved in the health technologies under comparison. Costs are defined as the quantities of resources

[5] The potential for bias are minimized and it is likely that a difference in costs or treatment effect between the two technologies is in fact caused by differences between the technologies.

multiplied by the unit costs of those resources. The second step in the costing process is the *measurement* of resource use in physical units, i.e. the determination of the quantities of resources. The third phase in the costing process is to *value* the unit costs of the resources used. Many researchers stress the importance of a separation between the measurement and the valuation of resource use - some because of the potential to use standard costs for valuation (e.g. Torrance et al. 1996). But probably the most important reason is that the separation of measurement and valuation facilitates the interpretation of results of a study from one setting to another, as both unit costs and quantities can vary by location. Ideally, the costing procedure adopted in an economic evaluation should be as transparent as possible so that users and readers of the economic evaluation (including decision-makers) can judge the relevance, precision and reliability of the cost data.

Several guidelines describe good standards for the identification, measurement, valuation and subsequent reporting of costs (Alban et al. 1998; CCOHTA, 1996; CCOHTA, 1997). In the Danish guidelines by Alban et al. (1998) it is stated that all relevant costs should be included. There should furthermore be a distinction between identification, measurement and valuation of the resource use. Indirect costs (similar to production loss) should be reported separately, and valuation should only be done if it is considered to be relevant. The three steps of identification, measurement and valuation of resource use were dealt with separately in the checklist and are described more thoroughly below.

Identification of resource use

When identifying the resource use of a health technology, *all* the relevant cost items and cost categories must be identified for later measurement and valuation. A common grouping of costs includes 1) costs within the health sector, 2) costs to patients and their families, 3) costs in other sectors. The checklist questions were based on this grouping, with the following subdivisions:

- Costs within the health sector
    - Inpatient care
    - Outpatient visits
    - Physician and other professional services in the primary health care sector
- Costs to patients and their families
    - Time consumed by patient and/or caregiver
    - Other resource use for the patient (e.g. out-of-pocket expenses related to a given treatment)
- Costs in other sectors
    - Home care/social care

The term ‘productivity loss’ is replaced here by the time consumed by the patient (i.e. work time consumed) and/or the caregiver (i.e. all time consumed) (Drummond et al. 1997a).

The perspective of the economic evaluation determines which costs should be included in the analysis. Table 2.6 illustrates this link between the perspective of the economic evaluation and the relevant cost categories.

Table 2.6
Cost categories and perspectives taken in economic evaluations

Common cost categories	Cost categories used in the review	Study perspective			
Costs in the health sector	Inpatient care	Hospital	Health care sector	Public sector	Societal
	Outpatient visits				
	Physician and other professional services in the health care sector				
Costs in other sectors	Home care and/or social care				
Costs to patient and family	Resource use for patients				
	Time consumed by patient and/or caregiver				

Note: Adaptation of Table 6.2 in Poulsen (2001)

Application of the societal point of view requires consideration of everyone affected by the intervention (e.g. a new treatment program) and counts all significant health outcomes and costs that result from it, regardless of who experiences the outcomes and costs. The costs thus include not only medical resources, but also the time of patients and unpaid caregivers.

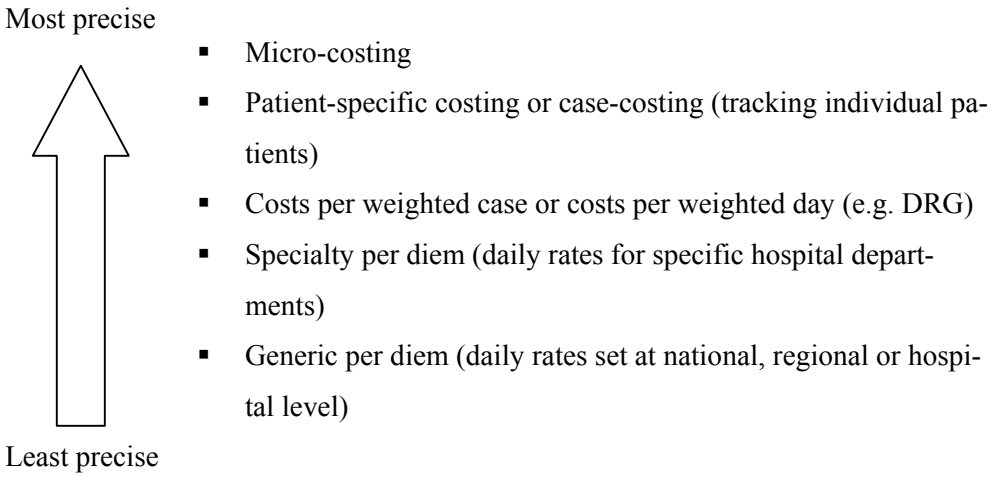
While economic evaluation aims to inform policy making from a broad societal perspective, health technology assessment and its accompanying economic evaluation are also directed at lower levels of decision-making, e.g. a hospital or the health care sector. In this case, an assessment of the costs and consequences from that perspective is relevant. Torrance et al. (1996) suggest that economic evaluation should be performed from several different perspectives, *including* that of society. Advocates of the societal perspective point out that even though an analysis with a narrower perspective (e.g. the hospital perspective) may lead to the same conclusions sometimes they do not, and the resulting recommendations may then not be optimal from a societal point of view. Furthermore, the societal perspective implicitly recognizes that societal resources are limited and that health should not be exempt from these restraints. In summary, although it may not be possible or necessary to measure and value all costs of the alternatives under comparison, a full identification of the important and relevant costs should be provided in an economic evaluation.

Measurement of resource use

The measurement of resource use requires determination of the quantities of resources used in the health technologies under comparison. The typical units for measuring resource use are physical units, such as time spent by health professionals, days of inpatient stay, medicine (type of drug and dosage level), number of tests, number of operations, number and duration of visits to a general practitioner, and days of absence from work. The sources for these data take different forms, but can be roughly grouped into primary and secondary data collection. *Primary data collection* refers to cost data that are prospectively collected specifically for the study at hand – what is labeled 'original data' in the checklist. In *secondary data collection*, the source of cost data can be studies in the literature, billings/administrative databases or expert opinion. For the purposes of the present review, the *major source* of data in the economic evaluation was recorded.

The relative importance of each item of resource use determines the level of detail required for the data collection. Figure 2.2 shows the level of precision of different costing approaches. A distinction can be made between micro-costing and macro-costing (gross costing) approaches. A *micro-costing approach* is the most precise, as each component of resource use is estimated and a unit cost is derived for it. The *macro-costing approach* is, in its most general form, the least precise of the costing approaches. It may involve the use of generic per diems, where daily rates set at the national, regional or hospital level are used to represent the average cost of, for example, one inpatient day.

Figure 2.2
Levels of precision in the costing of inpatient and outpatient care



Note: Adaptation of Box 4.6 in Drummond et al. (1997a) and Table 1 in CCOHTA (1996)

As Figure 2.2 shows, there are other costing approaches (e.g. costs per weighted case and specialty per diem), where the level of accuracy lies between the micro-costing and macro-costing approaches. There is a trade-off between the accuracy of the costing approach and the time and effort needed to obtain the cost estimate. The micro-costing approach is the most precise but also the most time-consuming to perform, while the collection of generic per diem rates requires much less effort and time but is also much less precise. Sometimes less precise measurement is sufficient, however, e.g. when the frequency of hospital stay is a more relevant factor than the intensity of care during the hospital stay.

Elliott (1997) notes that it is arguable whether to use charges (e.g. per diem rates) instead of actual costs (measured using the micro-costing approach), but recommends the collection of resource consumption data rather than charges. Drummond et al. (1997b) also recommend the use of real costs rather than charges, at least when the societal perspective is applied, since the real costs better reflect the opportunity costs of a given health technology.

When cost specification is conducted using a generic per diem approach (i.e. not patient-specific), it is said that the identification, measurement and valuation of costs is deterministic. If the economic evaluation is carried out alongside a clinical

study it is often possible to collect individual data on each patient's resource use. Then the specification of costs is said to be prospective and stochastic.

For the purposes of the present review, the assessment of resource use measurement for *inpatient and outpatient care* was based on the different costing approaches described above. For the measurement of *physician and other professional services in the health care sector*, it was decided to distinguish between micro-costing, patient-specific costing, costing on an hourly basis and cost per encounter. For resource measurement in *home care and/or social care* a distinction was made between micro-costing, costing on an hourly basis and cost per encounter, while *patient costs* are typically measured using either a questionnaire or a diary filled in by the patient. The costs of *time consumed* are typically measured using a human capital approach, in which the time consumed is valued according to the patients' wage rate. Some studies use the terminology of productivity losses or gains rather than time consumed. If productivity losses are measured, either the human capital approach or a friction cost approach can be applied when measuring the costs. The former assumes a productivity loss until the person either returns to work or retires/dies, whereas the friction cost approach assumes that productivity loss occurs only until the person can be replaced at work. For further information regarding these methods, see Koopmanschap & Rutten (1993).

Valuation of costs

The final step in costing requires the valuation of the quantities of resource by their unit prices. This should ideally be done by calculating the *opportunity cost* of the resources used, i.e. the benefit that could be obtained by the best alternative use of the resources. The opportunity cost is often difficult to estimate in practice, however, and therefore the *market price* is often used instead. It must be recognized, however, that prices in a health care market may not always reflect the opportunity costs. For example, drug prices are often artificially set through negotiations between a pharmaceutical company and the government. As a further example, wages in some countries are not determined in an open market, but by collective bargaining; in this case, the relevant cost estimate for an hourly wage (unit cost) would be the collectively agreed wage rate.

Market prices are only one way of valuing the costs of resource use. Others are charges, average costs and marginal costs. *Charges* may be substantially different from (opportunity) costs and are therefore not good approximations to the actual costs; they are often used, however, in cases where per diem rates are used to measure resource use. When real costs are measured as part of a micro-costing or a patient-specific costing approach, either marginal or average costs might be used. *Marginal costs*[6] are the costs that are expected to vary according to the number of patients treated, and express the cost of using one extra unit of resources. In comparison, *average costs* also include the resource use that does not vary with the number of patients treated, e.g. capital costs and other fixed costs. When comparing two or more health care programs it is important to decide how the costs should be estimated. In general, marginal (or incremental) costs are the most relevant, as the typical question being addressed is: 'What would be the costs (and consequences) of having a little more or a little less?' In other words, it is usually small changes in output that are being investigated.

[6] A distinction between marginal and incremental costs is important here: The *marginal costs* (MC) are the extra costs of producing one extra unit of output, whereas the *incremental costs* (IC) are the differences in costs between two health technologies.

2.4.4 Health outcomes

A health technology is applied when it is believed that the resultant consequences will improve the health status of patients. In economic evaluations, improvements in patients' health status can be either i) expressed in natural units (as in a cost-effectiveness analysis), ii) valued in utilities (e.g. quality-adjusted life-years (QALYs) or healthy years equivalents (HYE)) in a cost-utility analysis, or iii) expressed as preferences (e.g. as willingness-to-pay (WTP) or discrete choice or ranking) in a cost-benefit analysis. This section examines issues concerning the measurement of the health-related consequences of a health technology.

Identification, measurement and valuation of measures of effectiveness and health outcomes

In *cost-effectiveness analysis (CEA),* health outcomes are determined in 'natural units', which implies that a judgment of the value of the outcomes has not been made. Health outcomes in natural units can be divided into intermediate measures and final health outcomes. *Intermediate measures* are changes in health-related variables that are thought to be associated with the desirable outcome. Intermediate measures can be further divided into *surrogate measures,* such as changes in the values of clinical tests (e.g. ECG, mmHg, etc.), and *process measures* (e.g. cases detected/prevented, number of patients cured, admissions to hospital). Other intermediate measures are, for example, healthy days. Intermediate measures are typically clinically relevant measures that are less relevant for economic evaluation.

Final health outcomes are the health consequences from a technology in terms of, for example, lives saved, life-years gained, and changes seen on generic and disease-specific health status measures. Health outcome is the end result of the health technology under study, as opposed to the intermediate measures, which are indicators of this result. The final health outcome is often more relevant for economic evaluation than intermediate measures, as decision-makers are more interested in the effects of a health technology (e.g. treatment of high cholesterol level) in terms of lives saved and improvement of quality of life, rather than in clinical terms (e.g. the level of reduction in serum cholesterol level). As the time horizon for measurement of final health outcomes can be very long, however, intermediate measures are often used as proxies of final outcome, despite the frequent absence of an established association between the intermediate measure and the final health outcome.

When health consequences are measured in natural units, there is no valuation of the health outcomes. Such a valuation might be of relevance, however, where there are several dimensions that are of importance to the patients, e.g. not just improvement in health status, but also the level of information received, or the process of the treatment itself. This problem can be solved by using a preference-based measure of health-related quality-of-life, which can then allow the estimation of a utility measure, such as the quality-adjusted life-year (QALY). In a *cost-utility analysis (CUA)* approach, a single metric (e.g. QALY)[7] is established through a combination of health-related quality of life (morbidity) and quantity of life (survival). The QALY measure is thus two-dimensional since it considers both the quality and the quantity of life, whereas a cost-effectiveness analysis incorporates only one of these.

[7] Other measures such as the HYE can also be used.

QALYs can be calculated either through a method of eliciting preference weights (e.g. rating scale, time trade-off, standard gamble or person trade-off) or from pre-scored, multi-attribute health status classification systems (e.g. the EuroQol, 15D, HUI, Rosser Index or the QWB). Different questions regarding the methodologies apply to the two different methods of calculating QALYs. When the former method is used, the preferences are usually elicited from one of the following groups of people: patients, professional bodies/interest groups, informal caregivers, health professionals or society in general. When the latter measurement method is used, information is needed regarding which group (typically patients) identified health status in the pre-scored health status classification system.

Another way of valuing health outcomes is through *willingness-to-pay (WTP)*, which is used in cost-benefit analysis (CBA). Here the values and preferences for the health technology are estimated through people's (hypothetical) willingness to pay for the technology in question. The outcomes are measured in monetary units. CBA can also be based on other methods, such as the *human capital approach*, where the value of the treatment is assessed from the present value of future earnings for the patients in question. For further information concerning cost-benefit analysis and willingness-to-pay, the reader is referred to Bala et al. (1999) and Sugden & Williams (1978).

There is a natural hierarchy with regard to the use of health outcomes. The intermediate measures are regarded as the crudest way of measuring health outcome, followed by final health outcomes and then valuations of final health outcomes (e.g. through the use of QALYs) as part of a cost-utility analysis. At the top of the hierarchy is cost-benefit analysis, which is the only method of measuring health outcome that has a firm theoretical foundation.

2.4.5 Discounting

There is general agreement among economists that costs that arise in the future should be adjusted to take account of their different timing. There is ongoing debate as to whether health outcomes should also be discounted and indeed which assumptions should be made in terms of the timing of the added years of life or improved quality of life (Gyrd-Hansen & Søgaard, 1998). If only costs are discounted or if the benefits are discounted at a different rate than the costs, then the results of an economic evaluation may be inconsistent. If, for example, costs but not benefits were discounted in an evaluation of a preventive health technology that save future lives, the most cost-effective option would be to delay the implementation of the technology indefinitely, since the discounted costs that arise in the distant future will approach zero while the undiscounted benefits would be the same whether they accrue now or sometime in the distant future. It would then be rational to delay implementation indefinitely since a later implementation would give a lover cost per saved life.

There are several theoretical arguments in favor of discounting costs and health benefits occurring in the distant future in order to adjust for their timing. First, most people have positive time preferences, where an immediate gain (e.g. more money or better health) is preferred to the same gain in a year's time. This is related to the second argument, that future consumption involves both risk and uncertainty – we do not know whether we will be alive or dead in a year's time, and we do not know of our own wealth or how the price of goods (including health care) will develop over time. Positive time preference is therefore risk-avoiding behavior. The third argument is that, in a world where goods (including health care) have diminishing

marginal utility, the more we acquire of a good, the less we value the last unit acquired. The marginal value of future health care is therefore less than the value of health care today. The fourth argument is quite different and is based on the economic principle of opportunity cost. Wealth that we obtain today can be invested and will earn interest; if we first get the wealth in a year's time, this interest is forfeited.

The simple discounting formula converts a cost that arises in the future to its equivalent value if the cost arose today. Lower weight is thus assigned to costs and health outcomes that occur in the future, reflecting the general preference for future (rather than current) payment and current (rather than future) health outcomes. In economic evaluation, it is customary to use the discounting technique to convert a stream of annual costs and outcomes to an aggregated figure called net present value (NPV).

In adjusting for different timing of costs and benefits, the choice of discount rate is an important consideration. Theoretically, the discount rate should reflect society's time preference; in practice, however, this rate is unknown and is usually approximated using financial market rates or politically set discount rates that represent the minimum value for public investments. There is no general agreement on the most appropriate rate of discounting. According to Drummond et al. (1997b), 5% is common in the literature, but this is neither theoretically nor empirically justified. The US Panel on Cost Effectiveness in Health and Medicine (Siegel et al. 1997) recommends the use of a 3% discount rate, reflecting the interest rate of US government bonds, but also additional analysis with a 5% rate to allow comparison with other analyses; further sensitivity analyses using rates between 0 and 7% are also recommended. The Canadian guidelines (Torrance et al. 1996) recommend the use of a 5% discount rate, with sensitivity analysis to test the effect of this parameter. The Danish guidelines (Alban et al. 1998) do not state a particular discount rate, but instead recommend the use of a rate that is set (and adjusted when necessary) by the Ministry of Health, accompanied by appropriate sensitivity analyses.

2.4.6 Presentation of results

The way in which the results of an economic evaluation are presented is important in determining which health technology is more cost-effective (and therefore should be adopted). In both cost-effectiveness and cost-utility analysis, a useful way of presenting the results is to calculate and compare average *cost-effectiveness ratios* (cost-utility ratios) for each technology investigated. A cost-effectiveness ratio is defined as follows,

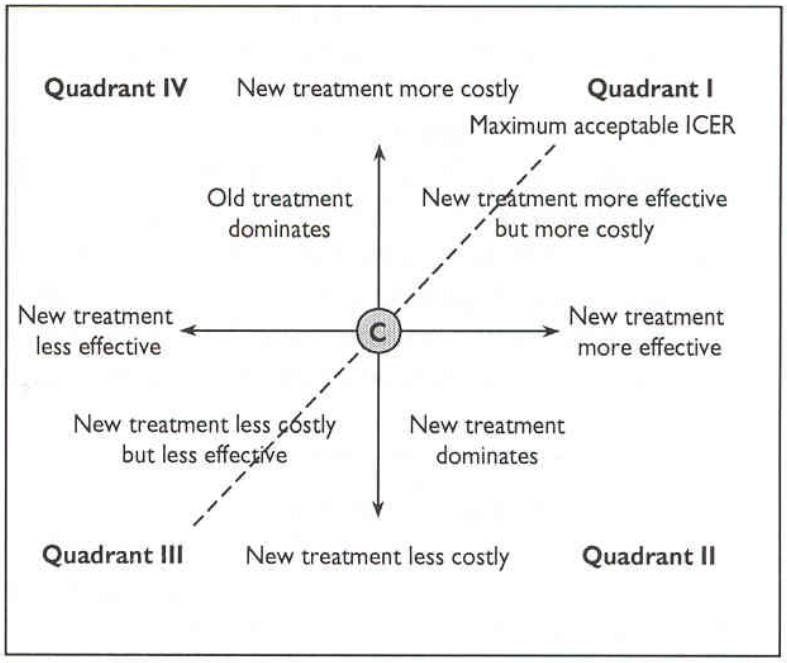
$$\frac{C}{E} = \frac{C_{(\text{health sector})} + C_{(\text{patients and family})} + C_{(\text{other sectors})} - \text{saved costs}}{\text{Effects}}$$

The effects may be measured in natural units (intermediate and final health outcomes) or, for cost-utility analysis, in utility-based measures (e.g. quality-adjusted life-years).

A comparison of the cost-effectiveness ratios of two alternative technologies can lead to various conclusions: If, for example, the new technology is more effective and at the same time is cheaper than the technology currently used, then it is clear that the new technology should be adopted. In this case, the new technology is said to be dominant (see quadrant II in Figure 2.3). If the new technology is more effec-

tive but also more expensive than current technology, however, the conclusion is less clear. In this case, there is no dominance, as illustrated in quadrant I in Figure 2.3. Quadrants III and IV in the figure illustrate similar situations, where the new technology is less effective (and either more or less costly) than the current technology.

Figure 2.3
The cost-effectiveness plane



Source: Briggs & Gray (1999)

When there is lack of dominance between two technologies, an incremental analysis should be performed in order to assess whether the extra effect that can be gained from the use of a new technology (or the old) is worth its extra cost. This incremental analysis can be undertaken by calculating the *incremental cost-effectiveness ratio* (ICER):

$$\text{ICER} = \frac{C_{(new)} - C_{(old)}}{E_{(new)} - E_{(old)}}$$

ICER expresses the extra costs of an extra unit of health outcome produced with the new technology compared to the old technology, e.g. the extra costs of gaining an extra life year. If, for example, the new technology is more effective but also more costly than the old technology, the decision about which technology to adopt will depend on the maximum price that the decision-maker is willing to pay for the extra health outcome. This is illustrated in Figure 2.3, where the dotted line represents the decision-maker's maximum willingness to pay. If the incremental cost-effectiveness ratio is to the right of the dotted line, then the new health technology should be adopted. This incremental cost-effectiveness ratio is more useful than the average cost-effectiveness ratio, as it allows alternatives to be prioritized. The average cost-effectiveness ratio compares the technology to the base case (no treat-

ment), while the ICER compares the health technology to the next best health technology.

When performing cost-benefit analysis, the outcomes (health benefits) are valued in monetary units. The conclusion about which technology to adopt can be made on the basis of the present value of the *net benefit*, which is defined as

$$\text{Net benefit} = \text{Benefits} - \text{Costs} \geq 0$$

If the benefits are greater than the costs, there will be a net benefit to society of adopting the technology. When two or more technologies are compared, the technology with the highest net benefit should be adopted.

The current review examined whether the major outcomes were presented in the form of a ratio (average cost-effectiveness ratio) or as net-economic benefit. It was also noted whether or not there was discussion of dominance and its relevance to the study, and whether incremental analysis of costs and outcomes was performed.

2.4.7 Sensitivity analysis

If the true values of all economic evaluation parameters were known, it would be possible to make a policy recommendation with full certainty. In practice, however, there is always some element of uncertainty in economic evaluation, which influences the robustness of the results and may alter the policy recommendation to choose one technology instead of another.

This section first briefly introduces the four main areas of uncertainty in economic evaluation. Approaches to handling uncertainty are then discussed – the use of sensitivity analyses for deterministic data, and the use of statistical analysis for stochastic data.

Areas of uncertainty

The central result of an economic evaluation is based on the most plausible estimates for the parameters included – this is the *base case*. By definition, these estimates are associated with some kind of uncertainty and thus the result of the economic evaluation also involves uncertainty. Uncertainty in economic evaluations arises from many different sources. Four main sources are described further here: 1) Uncertainty in data requirements, 2) Uncertainty relating to generalization, 3) Uncertainty relating to extrapolation, and 4) Methodological uncertainty.

Uncertainty in data requirements. This is the key source of uncertainty in economic evaluation, in which data are collected to both measure and value resource use and health outcome. Whether data are deterministic (point estimates) or stochastic (sample data), they are rarely able to reflect the normal variation that occurs within a population. Uncertainty in data requirements can arise, for example, from variation within the patient population as to their resource use, and from variations in unit costs and charges.

Uncertainty relating to generalization. Every economic evaluation is made within its own specific context with a well-defined group of patients. However, the researcher or decision-maker is often interested in generalizing the results to other contexts or other patient groups. The process of making assumptions about other contexts than that under study gives rise to uncertainty.

Uncertainty relating to extrapolation. Economic evaluations, and the clinical trials that they can be based on, are conducted over a defined, and often short, period of time. In order to estimate lifetime costs or lifetime health gains from the technology it is then necessary to extrapolate the results outside this period, thus including some uncertainty in the results.

Methodological uncertainty. As discussed earlier in this chapter, there is not full agreement among researchers about how economic evaluations ought to be performed. Opinions differ, for example, on issues such as the measurement of resource use and the valuation of outcome. The resulting variation in the methodology used in economic evaluations is a further source of uncertainty in the data.

Sensitivity analysis

The method used to handle uncertainty depends both on the type of data collected and the source of the uncertainty. For deterministic data (point estimates), the only way of handling uncertainty is to use sensitivity analysis. Four main types of sensitivity analysis are usually distinguished, as described below.

Simple sensitivity analysis. This is the most common form of sensitivity analysis, in which one or more of the components of an economic evaluation are varied across a plausible range of values in order to examine the effect on the results. In simple *one-way* sensitivity analysis only one parameter is varied at a time, while in simple *multi-way* sensitivity analysis two or more parameters are varied simultaneously. Simple sensitivity analysis can be used for handling all areas of uncertainty, the approach is easy to use and there are no restrictions in the choice of parameters to be varied. The simplicity of the approach can also be a disadvantage, however, as it does not reflect the complex nature of economic evaluation.

Threshold analysis. In threshold analysis, a specific input parameter is varied until a break-even point is reached. This break-even point occurs when the conclusion of the economic evaluation changes, e.g. to recommend the technology that was found to be less cost-effective in the base case.

Extreme scenario analysis. The starting point of extreme scenario analysis is the base case (that comprises the most plausible estimates for the parameters included). The next step is to choose the most optimistic and the most pessimistic values of all the inputs in the economic evaluation. In the most optimistic scenario, these are the lowest cost estimates and the highest health outcomes, while the most pessimistic scenario is based on the highest cost estimates and the lowest health outcomes. If a technology is preferred in the base case scenario as well as in the most optimistic and the most pessimistic scenarios, then the result of the economic evaluation is robust and the conclusion of the economic evaluation is relatively strong.

Probabilistic sensitivity analysis. Probabilistic sensitivity analysis uses both data and *a priori* information as inputs in the sensitivity analysis. In the three other types of sensitivity analysis described above, there is only limited recognition of the interdependency that exists between the parameters in an economic evaluation, and of the distributions of the parameters. Probabilistic sensitivity analysis aims at incorporating both these issues into sensitivity analysis. It is a more complicated approach, but can better reflect the complex nature of economic evaluation.

The different types of sensitivity analysis can be used to handle different kinds of uncertainty, as shown in Table 2.7. Simple sensitivity analysis is the most widely applicable, and can be used for all four types of uncertainty. Probabilistic sensitivity analysis can only be used to investigate variation in the data.

Table 2.7
The use of sensitivity analysis to handle different types of uncertainty

Sensitivity analysis	Uncertainty			
	Variation in data	Generalization	Extrapolation	Variation in methods
Simple sensitivity analysis	√	√	√	√
Threshold analysis	√	(√)	(√)	-
Analysis of extremes	√	(√)	(√)	-
Probabilistic analysis	√	-	-	-

Note: √ = applicable
(√) = only applicable in some cases
- = not applicable
Elaborated from Briggs et al. (1994)

Statistical analysis

The statistical approaches to handling uncertainty include partial stochastic analysis and full stochastic analysis. Partial stochastic analysis is used when either the cost or the outcome data possess stochastic properties. Full stochastic analysis is used when both sets of data possesses stochastic properties.

The present review recorded which area(s) of uncertainty was examined, and whether sensitivity analysis (including which type) or statistical analysis was used to handle the uncertainty. It was also recorded whether or not an explanation was given for the choice of parameters that were varied in the sensitivity analysis and for how the range of values for these parameters was chosen. It is clearly important to include *relevant* possible changes in parameters in a sensitivity analysis, rather than simply a random choice of parameters and ranges with no base in practice.

2.4.8 Discussion of results and methodology

The *discussion* section of an economic evaluation should help the reader interpret the results and should highlight issues of importance to users of the results. These issues include the methodology used in the study and it limitations, the relevance of comparison with other similar studies, the generalizability of the results to other patient groups or countries, the representativeness of the results for routine practice, and the issue of equity (e.g. in health, in access to health care, in use of health care). The present review recorded whether such issues were mentioned in the discussion section.

3 Results of the review of health economic evaluation in the general literature

The purpose of this chapter is twofold. First, the articles reviewed here helped in constructing the checklist for assessment of economic evaluation in HTA (see section 2.1), by providing both checklists and discussions of the relative merits of the various items that could be included in a checklist. Second, the information here on the methodology of economic evaluation in the health area in general can be used as a baseline with which to compare economic evaluation undertaken as part of HTA (Chapter 4).

3.1 Study frame

Type of economic evaluation

Table 3.1 lists the literature reviews in which the type of economic evaluation was a topic for review. Studies that reviewed other topics or that focused on a specific type of economic evaluation (e.g. the reviews of cost-utility analysis by Gerard (1992), Gerard et al. (1999), Gerard et al. (2000), and Stone et al. (2000) were excluded. As expected, the table shows that cost-effectiveness analysis, where the consequences are measured in natural units, e.g. life years gained, is the most frequent (61%) type of evaluation chosen for economic analyses within the health care sector. If the four studies reviewing cost-utility analyses were included, the proportion of this type of evaluation would increase slightly.

Table 3.1
Types of economic evaluation undertaken in the health care area

Literature review	Sam-ples	CMA[a]	CEA	CUA	CBA	Other[b]
Adams et al. (1992)	51	--	76%	--	16%	8%
Amin et al. (1998)	30	37%	13%	--	7%	43%
Anell & Norinder (2000)	455	--	80%	17%	3%	--
Briggs & Schulpher (1995)	93	12%	48%	11%	4%	25%
Chang & Henry (1999)	88	2%	42%	5%	52%	--
Evers et al. (1997)	91	41%	30%	2%	12%	15%
Evers et al. (2000)	23	48%	48%	4%	--	--
Ferraz et al. (1997)	36	--	92%	8%	--	--
Gambhir & Schwimmer (2000)	29	--	72%	28%	--	--
Jacobs & Fassbender (1998)	25	8%	92%	--	--	--
Kristiansen & Poulsen (2000)	30	90%	10%	--	--	--
Maetzel et al. (1998)	8	--	88%	12%	--	--
Rutten-Van Mölken et al. (1992)	20	20%	75%	5%	--	--
Morris et al. (1997)	38	--	87%	13%	--	--
Rothfuss et al. (1997)	44	61%	25%	--	7%	7%
Saleh et al. (1999a)	40	85%	12%	3%	--	--
Saleh et al. (1999b)	68	62%	22%	6%	10%	--
Salkeld et al. (1995)	33	--	55%	24%	21%	--
Schrappe & Lauterbach (1998)	40	--	55%	8%	37%	--
Taylor & Chrischilles (1997)	20	--	65%	35%	--	--
Udvarhelyi et al. (1992)	77	--	91%	--	9%	--
Walker & Fox-Rushby (2000)	107	5%	81%	5%	9%	--
Weatherly et al. (1999)	200	25%	58%	8%	1%	8%
Total (adjusted to total sample)	**1.646**	**16%**	**61%**	**10%**	**8%**	**5%**

a) Including cost analyses
b) E.g. cost-outcome analyses or cost-of-illness analyses

Perspective

The perspective of an economic evaluation should be explicitly stated. This is often not done, however. The reviews of Adams et al. (1992), Blackmore & Magid (1997), Blackmore & Smith (1998), Evers et al. (1997), Ferraz et al. (1997), Udvarhelyi et al. (1992) and Walker & Fox-Rushby (2000) reported a high number of economic evaluations (66–95%) in which the study perspective was not explicitly stated. However, two other reviews by Bradley et al. (1995) and Schrappe & Lauterbach (1998) found this to be a problem in only 23-25% of economic evaluations. Table 3.2 shows the frequency with which the different perspectives are used in economic evaluations in the health care sector.

Table 3.2
Perspective taken in economic evaluations in the health care area

Literature review	Sam-ples	So-cietal	Health system	Third party	Hospi-tal	Other	Not stated/ unclear
Adams et al. (1992)	51	6%	--	23%	43%	29%	--
Briggs & Schulper (1995)	93	29%	45%[a]	45%[a]	19%	2%	4%
Evers et al. (2000)	23	9%	--	--	--	--	91%
Gambhir & Schwimmer (2000)	29	14%	7%	7%	3%	7%	62%
Gerard (1992)	51	33%	59%	--	--	--	8%
Gerard et al. (1999)	43	12%	65%	--	--	19%	5%
Jacobs & Bachynsky (1996)	48	27%	--	--	13%	58%	2%
Kristiansen & Poulsen (2000)	30	7%	63%	--	30%	--	--
Saleh et al. (1999a)	40	5%	--	52%	23%	20%	--
Salkeld et al. (1995)	33	27%	70%	3%	--	--	--
Schrappe & Lauterbach (1998)	40	85%	--	3%	10%	3%	--
Slothuus (2000)	50	8%	20%	4%	62%	6%	--
Taylor & Chrischilles (1997)	20	55%	5%	15%	--	20%	5%
Walker & Fox-Rushby (2000)	107	9%	--	--	87%	8%	--
Weatherley et al. (1999)	200	10%	28%	--	39%	23%	--
Total [b] (adjusted)	**828**	**20%**	**25%**	**10%**	**33%**	**15%**	**6%**

a) 45% of the studies were based either on the perspective of the health system or that of the third party payer
b) Sums to more than 100 per cent as some studies used more than one perspective

Table 3.2 shows that the societal perspective is only adopted, on average, in 20% of the reviewed economic evaluations, even though this broad perspective is that recommended for economic evaluation. Only the reviews by Schrappe & Lauterbach (1998) and Taylor & Chrischilles (1997) report a much higher use of the societal perspective. Furthermore, it appears that the societal perspective is less commonly adopted in the studies reviewed more recently. The most frequently used perspective in economic evaluation is the narrower perspective of the hospital (health institution). This has implications for the costs that need to be measured as well as for the use of the analysis in decision-making.

Alternatives

Economic evaluation is a comparative analysis and thus the most likely alternatives e.g. other health technologies, should be taken into account. This seems to be well understood in the economic evaluations identified through the literature reviews, as between 71% and 100% of them include alternatives or comparators. Furthermore, Gerard et al. (1999) noted an improvement over time, with comparators being reported and appropriate in 81% of the studies reviewed in the period 1996-1998, as opposed to only 50% of the studies reviewed in the period 1980-1991.

3.2 Study design

The way in which the costs and consequences should be measured empirically is determined by the design of the economic evaluation. Economic evaluations have traditionally been based on retrospective data collection, but are increasingly being

conducted either alongside clinical trials with prospective data collection or following a predictive design in a modeling study, e.g. Markov modeling studies. Study design can be difficult to assess from journal articles and was a topic for review in only a few of the literature reviews. Table 3.3 presents the results for these studies.

Table 3.3
Study design in economic evaluations in the health care area

Literature review	Samples	Prospective (RCT/not)	Retrospective	Predictive (modeling)	Mixed/ other	Unclear
Adams et al. (1992)	51	76%	26%	--	--	--
Agro et al. (1997)	90	34%	27%	43%	6%	--
Briggs & Schulper (1995)	93	39%	18%	24%	40%	3%
Briggs & Gray (1999)	337	14%	9%	76%	--	--
Gerard (1992)	51	41%	14%	--	4%	41%
Jacobs & Fassbender (1998)	25	36%	--	64%	--	--
Stone et al. (2000)	228	33%	--	--	--	--
Taylor & Chrischilles (1997)	20	5%	--	90%	--	5%
Total [a] (adjusted)	**895**	**29%**	**10%**	**39%**	**5%**	**3%**

a) Does not sum to 100% as type of design was not reported for all economic evaluations reviewed

Table 3.3 shows that predictive (modeling) studies are the most frequent design chosen, followed by prospective designs.

3.3 Costing

Costing issues are usually a main focus of economic evaluations. As was seen in Table 2.5 in Chapter 2, six of the literature reviews identified here reviewed only cost measurement in economic evaluations.
Table 3.4 summarizes the findings for two basic requirements in economic evaluations – the presence of a clear statement about how costs were estimated or measured, and a description of the sources used to obtain these cost data.

Table 3.4
Statement on measurement and source of cost data in economic evaluations in health care

Literature review	Samples	Clear statement of *measure* of cost	No clear statement of *measure* of cost	Statement of *source* of cost data	No statement of *source* of cost data
Blackmore & Magid (1997)	44	98%	2%	70%	30%
Blackmore & Smith (1998)	56	98%	2%	82%	18%
Chang & Henry (1999)	88	99%	1%	--	--
Gerard (1992)	51	63%	27%	61%	21%
Gerard et al. (1999)	43	21%	79%	--	--
Smith & Blackmore (1998)	98	95%	5%	65%	35%
Weatherly et al. (1999)	200	73%	27%	57%	43%
Total (adjusted)	**580**	**80%**	**19%**	**64%**	**36%**

There seem to be few problems with making a clear statement about how the costs in an economic evaluation were measured. The only exception to this finding is a review by Gerard et al. (1999), who found that a clear statement of cost measurement was included in only 9 of 43 (21%) cost-utility analyses published in 1996. The same authors concluded that the appropriate reporting of cost methods had fallen by 40% compared to previous findings (Gerard, 1992) and that insufficient cost reporting occurred most commonly in specialist medical journals. However, other recent reviews of articles in specialist medical journals (e.g. Chang & Henry, 1999; Smith & Blackmore, 1998) did not support this conclusion. Table 3.4 also shows that the sources of cost data were not stated in 36% of the economic evaluations reviewed, a finding that makes it difficult to judge the appropriateness of the cost data used in these studies.

The type of costs included in the economic evaluations reviewed is summarized in Table 3.5. Most of the economic evaluations included some sort of direct health care costs. In three of the four reviews these direct health care costs were further subdivided. The resource use in connection with hospital inpatient care was the most frequent type of cost measured. The finding of Kristiansen & Poulsen (2000) that outpatient costs were more frequently reported is explained by their focus on telemedicine, which is practiced mainly in outpatient clinics.

Table 3.5
Types of costs identified and measured in economic evaluations in health care

Literature reviews	Samples	Direct health care costs[a] 1) in & 2) outpatients, 3) physician	Home care/ social care	Patient costs	Loss of productivity
Jacobs & Bachynsky (1996)	48	1) 85% 2) 25% 3) 88%	6%	8%	19%
Kristiansen & Poulsen (2000)	30	1) 30% 2) 63% 3) --	--	60%	3%
Slothuus (2000)	50	1) 78% 2) 48% 3) 50%	4%	6%	8%
Stone et al. (2000)	228	1) 87% 2) 73% 3) --	17%	5%	8%
Evers et al. (1997)	91	100%	16%	--	31%
Evers et al. (2000)	23	100%	--	17%	8%
Ganiats & Wong (1991)	47	100%	--	--	14%
Gerard (1992)	51	88%	--	--	10%
Maetzel et al. (1998)	8	100%	13%	--	25%
Morris et al. (1997)	38	100%	--	5%	5%
Rutten et al. (1992)	20	100%	--	16%	5%
Walker & Fox-Rushby (2000)	107	100%	--	7%	9%
Weatherly et al. (1999)	200	100%	12%		10%
Total [b] (adjusted)	**941**	**92% 85% 71%**	**9%**	**8%**	**11%**

a) In the first four studies, the direct health care costs were divided into inpatient, outpatient and physician care costs
b) Does not sum to 100% as more than one type of cost was identified and measured in the economic evaluations

In the review by Stone et al. (2000), inpatient care was divided into costs related to the intervention (reported by 97% of studies) and costs related to hospitalization (87% of studies). Only a few economic evaluations have identified and measured both costs related to social care or home care and patient costs. The only literature review reporting a high frequency of patient costs measured in economic evaluations is that by Kristiansen & Poulsen (2000). Again, their focus on telemedicine explains this difference, as the high costs for patients to travel from remote areas to attend for treatment in hospital were used in 18 out of 30 (60%) economic evaluations as an important argument for introducing telemedicine as a cost-saving alternative. For the purposes of comparison, only 5% of the economic evaluations reviewed by Stone et al. (2000) included transportation costs.

Productivity loss in society due to disease, disability and death was, on average, only included in 11% of the economic evaluations reviewed (Table 3.5). This could be in accordance with the chosen study perspective, however, as concluded by Weatherly et al. (1999). Productivity loss can be measured for patients as well as for their relatives (e.g. if family members take days off work to look after the patient). The literature review by Jacobs & Fassbender (1998) reported that 21 of 25 studies had measured productivity loss for patients, and that 8 studies had measured the same for caregivers. Jacobs & Bachynsky (1996) reported that nine studies (19%) included productivity loss for patients and four studies (8%) for caregivers as well. Weatherly et al. (1999) reported that the human capital approach was used

in 18 of 20 studies estimating productivity loss, while Jacobs & Fassbender (1998) found this to be the case in all studies. In both reviews, only two studies had adopted the friction cost approach.

Some of the literature reviews assessed whether the economic evaluations used *appropriate* cost measures. The results from Adams et al. (1992; 24%), Lee & Sanchez (1991; 31%) and Salkeld et al. (1995; 45%) were not optimistic. Slothuus (2000) concluded that, in general, the economic evaluations that were reviewed did not include the costs that were relevant to the chosen perspective.

A description of the source of cost data is important in determining how the resource use should be valued. Table 3.6 reveals considerable variation with respect to the sources of cost data used in economic evaluations, and more than one source is often used in a single study. Frequent cost sources appear to be original data, data published by the government or a hospital, and billing or charges data (e.g. retail prices, fee schedules, hospital charges). Evers et al. (1997) and Evers et al. (2000) found that 70% and 26%, respectively, of economic evaluations used charges as proxies for costs. This is not unproblematic, as charges typically relate to a specific institution's budget and do not express the opportunity cost of an activity. Cost estimates from previous studies as well as from expert opinion or guesses have also been used as sources for cost data in economic evaluations.

Table 3.6
Sources of costs used in economic evaluations in health care

Literature review	Samples	Original data	Studies in the literature	Billings/ charges	Expert opinion	Other	Unclear
Briggs & Schulper (1995)	93	45%	27%	16%	--	6%	25%
Morris et al. (1997)	38	3%	26%	82%	13%	8%	5%
Stone et al. (2000)	228	Health 73% Other 45% Produc. 68%	--	Health 54% Other 3% --	Health 25% Other 26% Produc. 26%	Health 35% Other 18% Produc. 16%	Health 8% Other 18% Produc. 5%
Weatherly et al. (1999)	200	35%	8%	18%	--	20%	19%

3.4 Health outcomes

As Table 3.7 shows, health outcomes tend to be measured in natural units. This is a logical consequence of the majority of studies being cost-effectiveness analyses (see section 3.1). More than half the studies used intermediate measures of effectiveness, as opposed to 25% that used a final health outcome (life years gained or lives saved) and 13% that used a QALY measure.

Table 3.7
Health outcome measures used in economic evaluations in health care

Literature review	Samples	Intermediate measures	Life years gained or lives saved	QALY (CUA)	Monetarized (CBA)	Other
Anell & Norinder (2000)	455	51%	26%	15%	1%	6%
Evers et al. (2000)	23	43%	48%	4%	--	30%
Ferraz et al. (1997)	36	38%	3%	28%	--	31%
Gambhir & Schwimmer (2000)	29	48%	24%	28%	--	--
Jacobs & Fassbender (1998)	25	24%	16%	16%	--	20%
Kristiansen & Poulsen (2000)	3	100%	--	--	--	--
Morris et al. (1997)	38	36%	56%	8%	--	--
Schrappe & Lauterbach (1998)	40	80%	13%	7%	--	--
Taylor & Chrischilles (1997)	20	20%	20%	35%	--	30%
Walker & Fox-Rushby (2000)	107	78%	23%	--	9%	29%[a]
Total [b] (adjusted)	**776**	**53%**	**25%**	**13%**	**2%**	**11%**

a) Among these studies, 87% used resources saved as outcome measures
b) Does not sum to 100% as more than one type of outcome measure was used in some economic evaluations

The frequent use of intermediate measures of effectiveness is a problem, as these measures are less relevant for economic evaluation (although they are clinically relevant, as discussed in section 2.4.4). Of course, generalization from the results in Table 3.7 should only be done very cautiously, since some of the economic evaluation studies might have been included in more than one of the reviews listed in Table 3.7, as discussed in section 2.3

Anell & Norinder (2000) found that the choice of health outcome measure differed across disease categories. For example, QALYs were used more often in studies relating to neoplasms (24% of the cases) than in studies relating to the digestive system (5% of cases). Furthermore, they found no evidence that QALYs or life-years gained have become more common over the years; although the absolute number of studies using these approaches have risen, the relative share of economic evaluations using QALYs or life-years gained has fallen from 1986 to 1996.

3.5 Discounting

There appears to be great variability among economic evaluation studies regarding the use of discounting for future costs and outcomes (Table 3.8). The results of several reviews (Chang & Henry, 1999; Gerard, 1992; Schrappe & Lauterbach, 1998; Taylor & Chrischilles, 1997) imply a relatively high use of discounting, while others (Adams et al, 1992; Amin et al, 1998; Kristiansen & Poulsen, 2000; Lee & Sanchez, 1991; Smith & Blackmore, 1998) demonstrate infrequent use of discounting. The range of use, 0% to 77%, indicates major differences in practice between economic evaluations and suggests that too few economic evaluations emphasize discounting of future costs and health outcomes.

Few reviews assessed the inclusion of discussion about the chosen discount rate, the exceptions being Salkeld et al. (1995) and Weatherly et al. (1999).

Table 3.8
Use of discounting in economic evaluations in health care

Literature review	Samples	% of studies *with* discounting (costs & consequences)	% of studies *without* discounting	% of studies appropriately not discounted
Adams et al. (1992)	51	a) 6%, b) 0%	a) 16%, b) 18%	a) 78%, b) 82%
Allred et al. (1998)	7	0%	100%	--
Amin et al. (1998)	30	3%	97%	--
Blackmore & Magid (1997)	44	a) 11%	a) 89%	--
Blackmore & Smith (1998)	56	32%	68%	--
Brown & Schulper (1999)	29	b) 52%	b) 48%	--
Chang & Henry (1999)	88	69%	31%	--
Evers et al. (1997)	91	24%	57%	19%
Ferraz et al. (1997)	36	17%	83%	--
Gambhir & Schwimmer (2000)	29	21%	72%	7%
Gerard (1992)	51	71%	14%	10%
Kristiansen & Poulsen (2000)	30	7%	93%	--
Lee & Sanchez (1991)	65	3%	19%	78%
Maetzel et al. (1998)	8	50%	12%	38%
Morris et al. (1997)	37	61%	19%	29%
Rothfuss et al. (1997)	44	36%	--	64%
Rutten-Van Mölken et al. (1992)	20	15%	35%	45%
Salkeld et al. (1995)	33	48%	15%	33%
Schrappe & Lauterbach (1998)	40	79%	--	21%
Slothuus (2000)	50	a) 52%	a) 48%	--
Smith & Blackmore (1998)	98	10%	90%	--
Stone et al. (2000)	228	a) 73%	a) 16%	a) 11%
Taylor & Chrischilles (1997)	20	85%	5%	10%
Udvarhelyi et al. (1992)	77	18%	20%	62%
Walker & Fox-Rushby (2000)	107	35%	16%	50%
Weatherly et al. (1999)	200	30%	9%	61%
Total (adjusted)	**1.569**	**36%**	**34%**	**28%**

Only costs, b) Only consequences (health outcomes)

3.6 Presentation of results

It is important to present the results of a study in a way that can guide decision-makers in choosing between two or more alternative health technologies. One way of doing this is to calculate the average cost-effectiveness ratios for each alternative technology. An adjusted total of 65% of the reviewed economic evaluation studies presented the results as cost-effectiveness ratios (Table 3.9). However, this result covers a wide range: between 9% (e.g. reported by Evers et al. 2000) and 100% of studies calculated cost-effectiveness ratios.

Table 3.9
Use of a summary measure (cost-effectiveness ratio or net-benefit) in economic evaluations in health care

Literature review	Samples	Yes	No
Allred et al. (1998)	7	100%	0%
Blackmore & Magid (1997)	44	41%	59%
Blackmore & Smith (1998)	56	48%	52%
Briggs & Schulper (1995)	93	72%	28%
Chang & Henry (1999)	88	91%	9%
Evers et al. (2000)	23	9%	91%
Gambhir & Schwimmer (2000)	29	59%	41%
Salkeld et al. (1995)	33	73%	27%
Smith & Blackmore (1998)	98	57%	43%
Udvarhelyi et al. (1992)	77	42%	58%
Walker & Fox-Rushby (2000)	97	90%	10%
Total (adjusted)	**645**	**65%**	**35%**

As shown in Table 3.10, only a quarter of the economic evaluation studies calculated an incremental cost-effectiveness ratio. Again, this result covers a wide range. Lee & Sanchez (1991) found that only 2% of the studies performed incremental cost-effectiveness analysis, while Ferraz et al. (1997) reported that 64% of the economic evaluations calculated incremental cost-effectiveness ratios.

Table 3.10
Incremental analysis in economic evaluations in health care

Literature review	Samples	Yes	No
Amin et al. (1998)	30	7%	93%
Blackmore & Smith (1998)	56	39%	61%
Chang & Henry (1999)	88	14%	86%
Evers et al. (2000)	23	17%	83%
Ferraz et al. (1997)	36	64%	36%
Gambhir & Schwimmer (2000)	29	52%	48%
Lee & Sanchez (1991)	65	2%	98%
Maetzel et al. (1998)	8	63%	37%
Rothfuss et al. (1997)	11	18%	82%
Schrappe & Lauterbach (1998)	40	53%	47%
Smith & Blackmore (1998)	98	17%	83%
Udvarhelyi et al. (1992)	32	31%	69%
Walker & Fox-Rushby (2000)	97	30%	70%
Total (adjusted)	**613**	**27%**	**73%**

3.7 Sensitivity analysis

Table 3.11 displays the considerable variation found among studies regarding the use of sensitivity analysis. Some reviews report a high use of sensitivity analysis in economic evaluations (e.g. Bradley et al., 1995; Maetzel et al., 1998; Salkeld et al., 1995; Taylor & Chrischilles, 1997), while others report a very low use (Blackmore & Magid, 1997; Evers et al., 1997; Lee & Sanchez, 1991). Gerard et al. (1999) detected an increase in the use of sensitivity analysis from the 1980-1991 period to 1996, while Ganiats & Wong (1991) reported a greater use of sensitivity analysis in cost-effectiveness analyses than in cost-benefit analyses.

Table 3.11
Use of sensitivity analysis in economic evaluations in health care

Literature review	Samples	Yes	No
Agro et al. (1997)	90	59%	41%
Allred et al. (1998)	7	29%	71%
Amin et al. (1998)	30	17%	83%
Blackmore & Magid (1997)	44	18%	82%
Blackmore & Smith (1998)	56	24%	76%
Bradley et al. (1995)	90	88%	12%
Briggs & Schulper (1995)	93	54%	46%
Briggs & Gray (1999)	337	83%	17%
Brown & Schulper (1999)	29	62%	38%
Chang & Henry (1999)	88	47%	53%
Evers et al. (1997)	91	10%	90%
Evers et al. (2000)	23	17%	83%
Ferraz et al. (1997)	36	64%	36%
Gambhir & Schwimmer (2000)	29	66%	34%
Jacobs & Bachynsky (1996)	48	62%	38%
Kristiansen & Poulsen (2000)	30	40%	60%
Lee & Sanchez (1991)	65	6%	94%
Maetzel et al. (1998)	8	75%	25%
Morris et al. (1997)	37	65%	35%
Rutten-Van Mölken et al. (1992)	20	15%	85%
Salkeld et al. (1995)	33	76%	24%
Schrappe & Lauterbach (1998)	40	58%	42%
Slothuus (2000)	50	68%	32%
Smith & Blackmore (1998)	98	21%	79%
Stone et al. (2000)	228	66%	34%
Taylor & Chrischilles (1997)	20	95%	5%
Udvarhelyi et al. (1992)	77	30%	70%
Walker & Fox-Rushby (2000)	107	43%	57%
Weatherly et al. (1999)	200	39%	61%
Total (adjusted)	**2104**	**52%**	**48%**

Table 3.12 shows that the most common type of sensitivity analysis used in the economic evaluations reviewed was the simple one-way sensitivity analysis. The most seldom used was probabilistic sensitivity analysis, possibly because of the greater complexity of this method.

Table 3.12
Type of sensitivity analysis used in economic evaluations in health care

Literature review	One-way	Multi-way	Threshold	Extreme	Probabil-istic	Confidence Intervals
Agro et al. (1997)	41%		11%	10%	4%	10%
Briggs & Schulper (1995)	84%	30%	24%	10%	2%	--
Briggs & Gray (1999)	72%	16%	13%	6%	2%	5%
Brown & Schulper (1999)	65%	35%	--	--	--	--
Evers et al. (2000)	--	--	--	--	--	70%
Maetzel et al. (1998)	83%	50%	--	50%	--	--
Walker & Fox-Rushby (2000)	96%	33%	20%	--	2%	--
Weatherly et al. (1999)	61%	8%	7%	5%	1%	38%

4 Results of the HTA literature review

This chapter presents the results of the literature review relating to economic evaluations undertaken as part of health technology assessment (HTA). Sixty-seven HTA economic evaluations have been reviewed according to a checklist of topics developed specifically for the current purpose. For a discussion of these topics, including their theoretical background, the reader is referred to section 2.4.

4.1 Study frame

General HTA-related topics

Of the 67 HTAs reporting economic evaluations undertaken as part of HTA, 94% (64 HTAs) included clinical considerations, 30% (20 HTAs) included organizational parameters, 27% (18 HTAs) included patient-related parameters, and one was a cost analysis with no clinical, organizational or patient parameters included (Table 4.1).

Table 4.1
Key parameters assessed in HTA economic evaluations

Key topic	N
Economic evaluation	67
Clinical issues	64
Organizational issues	20
Patient-related issues	18

The comprehensiveness of a HTA is defined in relation to the number of parameters included. A comprehensive HTA is one that includes all four parameters - economic, clinical, patient-related and organizational aspects (Poulsen & Hørder, 1998). The literature review thus demonstrates that only 20% (13) of the HTAs identified could be considered as comprehensive health technology assessments; among these are 4 Danish HTAs. Partial HTAs were most commonly performed: 15% (10) of the HTAs included three of the aspects and a further 54% (36) included two parameters. It can be argued, however, that comprehensiveness is a secondary consideration – a factor of more importance is whether the form of the HTA is useful for the decision-problem at hand. This aspect was not investigated further, however, in the current review.

Table 4.2 shows the types of intervention that were assessed in the 67 HTAs. More than 50% of the HTAs investigated *treatments*, e.g. Oh et al. (1997) examined the use of Risperidone in the treatment of chronic schizophrenia. A smaller number of HTAs assessed *screening* and *preventive procedures* (15% and 13%, respectively). For example, the Swedish Council on Technology Assessment in Health Care – SBU (1996) examined the prevention of coronary heart disease and hip fractures by use of hormone replacement therapy, while Leivo et al. (1999) analyzed a screening program for breast cancer. Only 5 (8%) HTAs examined *diagnostic procedures* (e.g. Lindberg et al. (1990) assessed the use of gastroscopy in the diagnosis of dyspepsia). None of the HTAs assessed nursing care. 'Other' types of intervention included rehabilitation (e.g. Cameron et al., 2000) and patient education (e.g. Lord et al., 1999).

Table 4.2
Type of intervention assessed in HTA economic evaluations

Intervention	N	Percent
Treatment	37	55
Screening	10	15
Prevention	9	13
Diagnostic	5	8
Nursing care	0	0
Other	6	9
Total	**67**	**100**

As can be seen in Table 4.3, most (74%) of the technologies assessed were procedures. This result may have been affected by the absence of a clear distinction between a 'procedure' on the one hand and 'drugs' and 'devices' on the other. Although an attempt was made to define these terms, they may not have been mutually exclusive. Another possible explanation is that a device may be seldom assessed in a HTA, but this is not supported by the findings of an international comparison (Poulsen, 1999), in which 74 (60%) of 124 HTAs assessed procedures, 32 (26%) assessed devices, and 18 (15%) assessed pharmaceuticals.

Table 4.3
Type of health care technology assessed in HTA economic evaluations

Technology	N	Percent
Drug	16	24
Device	1	2
Procedure	50	74
Total	**67**	**100**

Outline of the economic evaluation

The purpose of the study was stated in all 67 HTAs. Some HTAs were very specific (e.g. Lindberg et al. (1990) stated that '*the purpose was to examine how endoscopy was doing with regard to costs and effectiveness compared to alternative methods in the area of gastroscopy in the diagnosis of dyspepsia')*, while others were less specific (e.g. Murray et al. (1997) noted that '*the purpose was to provide information needed to decide whether to use DNA-testing to screen for fragile X syndrome'*. The judgment as to whether a study's purpose is sufficiently described is, of course, highly subjective.

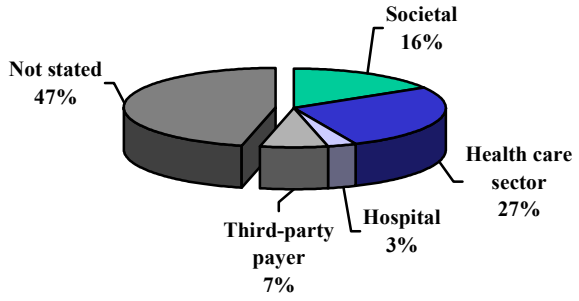
Half the HTA economic evaluations were performed as cost-effectiveness analyses only, whereas 6% were cost-utility analyses only (Table 4.4). In 10% of the HTAs, both cost-effectiveness analysis and cost-utility analysis were performed. Cost-benefit analysis was seldom used, and only in conjunction with cost-effectiveness analysis (and cost-utility analysis in a couple of cases). Cost-minimization or cost-analysis was quite widely used, being performed in almost one-third of the HTAs.

Table 4.4
Type of economic evaluation performed in HTA economic evaluations

Economic evaluation	N	Percent
Cost-effectiveness (CEA)	33	49
Cost-utility (CUA)	4	6
Both CEA and CUA	7	10
Both cost-benefit (CBA) and CEA	1	2
Both CEA and CUA and CBA	1	2
Cost minimization/cost analysis	19	28
Cost-outcome	2	3
Total	**67**	**100**

Figure 4.1 illustrates the perspectives taken in the HTAs. More than one quarter of the HTAs (27%) performed the economic evaluation from the perspective of the health care sector, while 16% applied the perspective of society and only 7% and 3% applied the perspective of a third party payer and the hospital/department, respectively. No HTA included an economic evaluation performed from the perspective of the public sector or that of the patient. The perspective was not stated in 47% of the HTAs.

Figure 4.1: Perspective of economic evaluation (N=67)



In only one of the 67 HTAs was a comparator not defined and applied. An example of a typical design of an economic evaluation undertaken as part of a HTA is described in Box 4.1.

Box 4.1 An example of the design of an economic evaluation
In a Canadian study by Ilersich (1997), the purpose of the study was stated explicitly in a research question: "*At what minimum risk of febrile neutropenia are the benefits of G-CSF attained at no additional cost, and what is the incremental cost of avoiding one case of febrile neutropenia in the Canadian health care system?*"
In the research question, the perspective of the analysis is stated to be that of the **health care system**. The economic evaluation was performed as a **cost-effectiveness analysis** comparing G-CSF to the **alternative** standard antimicrobial therapy with no G-CSF.

4.2 Study design

In most (85%) of the HTAs the economic data were collected retrospectively in relation to the clinical data collection, as has been the tradition in economic evaluation. In 9 HTAs (13.5%) the data were collected prospectively alongside a clinical trial (e.g. Grieve et al., 1999), and in one HTA (Tuulonen et al., 1999) there was no clinical data collection.

A primary source of clinical evidence was used in only 30% (20) of HTAs, either as a randomized controlled trial (RCT) or another primary study (Table 4.5). Secondary sources of evidence were used in 70% of HTAs, usually in the form of a meta-analysis of RCTs and/or non-RCTs. Quite a few HTAs based their evidence on non-systematic reviews, however, which is of concern as this data source is not considered sufficiently reliable for the purpose (Liberati et al., 1997).

Table 4.5
Collection of clinical evidence in HTA economic evaluations

Method of collecting evidence	N	Percent
Primary methods:		
RCT	6	9
Other primary method	13	19
RCT *and* other primary method	1	1.5
Secondary methods:		
Meta-analysis (of RCT's and/or non-RCT's)	16	24
Systematic review	10	15
Unsystematic review	14	21
Expert panel	2	3
Public files/databases	1	1.5
Systematic review *and* expert panel	1	1.5
Meta-analysis *and* expert panel	2	3
Not clear/not stated	1	1.5
Total	**67**	**100**

The issue of sample size was examined for the clinical study and the economic evaluation separately. Just over 60% (41) of the HTAs comprised population studies or types of modeling (e.g. scenario analyses), for which sample size calculation was not relevant. In 30% (20) of the HTAs, sample size was stated for either the clinical study or the economic evaluation but the method of calculation was not reported. Only two HTAs reported that sample size had been calculated for the clinical part of the study, while sample size was neither calculated nor stated in two HTAs, and it was unclear in two further HTAs. It was not possible to conclude that any of the HTAs calculated the optimal sample size. It should be noted that sample size might have been calculated for the clinical part of the HTA without it being reported in the economic evaluation - the very low number of HTAs where sample size is stated for the clinical study may therefore be an underestimation of the true number of HTAs with sample size calculations.

Almost two-thirds of the HTAs used some type of modeling approach in the economic evaluation (Table 4.6). The most common modeling technique was a decision tree (48% of HTAs), whereas Markov modeling was used more seldom (6%). Box 4.2 describes a typical study design based on a modeling approach.

Table 4.6
Modeling approaches used in HTA economic evaluations

Type of model	N	Percent
Modeling was not used	23	34
Decision tree	31	46
Markov model	3	5
Both decision tree and Markov model	1	2
Other model	7	10
Not stated/not clear	2	3
Total	**67**	**100**

Box 4.2 An example of study design
The Canadian study by Ilersich (1997), which is also mentioned in Box 4.1, is a typical example of a modeling study. The clinical evidence was obtained from phase III randomized controlled trials (it is not apparent whether a systematic literature review was performed) as a **secondary source for the clinical evidence**. The cost data were collected **retrospectively** from previous economic studies undertaken in the same field. These data were combined in a **decision analytical model** using a decision tree.

4.3 Costing

Separation of identification, measurement and valuation of resource use

The methods of identifying, measuring and valuing resource use should have been described separately in the evaluation reports. This was done in 51% (34) of the HTAs. In 27% (18) of the HTAs, there was no explicit separation between resource use and unit costs, while in a further 22% (15) of the HTAs this distinction was not always explicit. This makes it difficult to evaluate the appropriateness of the cost estimates, and whether possible biases in the costing process have been avoided. Separation is also important in generalizing the findings of an economic evaluation to other contexts where, for example, prices for the resource units may be different.

Costs within the health sector

Costs related to inpatient and outpatient treatment were identified in 67% and 66% of the HTA economic evaluations, respectively, whereas costs related to primary care and home/social care were identified in 39% and 12% of HTAs, respectively (Table 4.7).

Table 4.7
Identification of resource use within the health sector in HTA economic evaluations

	Inpatient care		Outpatient care		Primary care		Home care and/or social care	
	N	Percent	N	Percent	N	Percent	N	Percent
Identified	45	67%	44	66%	26	39%	8	12%
Not identified	21	31%	23	34%	40	60%	59	88%
Not relevant according to the authors	1	2%	0	0%	1	1%	0	0%
Total	67	100%	67	100%	67	100%	67	100%

When the societal perspective is applied in an economic evaluation, all cost components should be identified, or at least stated to be irrelevant. It may well be that for many of the economic evaluations where inpatient costs were not identified (n=21+1), this may be justified by the inpatient cost component being irrelevant – for example, see Box 4.3. In these cases, however, the cost component should still be identified, with a clear statement that they were considered to be irrelevant to the current purpose.

Box 4.3 Diabetic retinopathy – the value of early detection (SBU, 1993)
In this health technology assessment of a program to screen people with diabetes for retinopathy (i.e. disorder/changes in the retina), the economic evaluation focuses on the cost-effectiveness of early detection of retinopathy.
As the screening, diagnostics and treatment of retinopathy are all performed in outpatient departments, the identification of inpatient costs is not relevant. The economic evaluation therefore correctly identifies only outpatient costs and costs due to loss of production. The report does not explicitly state, however, that inpatient costs were irrelevant.

Original data were the major source of cost data in 37% (25) of the HTA economic evaluations, while studies in the literature were the major source in a further 37% of the HTAs (see also Table 4.11). Inpatient and outpatient costs (when identified) were typically measured using micro-costing, patient-specific costing, case-costing or 'other method'[8] (Table 4.8). The method of measuring inpatient and outpatient costs was either not stated or was unclear in a relatively large number of cases (13% and 16%, respectively).

[8] The notation 'other method' typically implies that cost measurement was based on estimates (expert judgment).

Table 4.8
Measurement of inpatient and outpatient costs in HTA economic evaluations

	Inpatient costs		Outpatient costs	
	N	Percent	N	Percent
Micro-costing	13	19%	13	19%
Patient-specific costing or case-costing	8	12%	3	4%
Costs per weighted case or costs per weighted day	4	6%	1	2%
Specialty per diem	3	4%	1	2%
Generic per diem	0	0%	0	0%
Patient-specific costing and generic per diem	1	2%	1	2%
Micro-costing and other method	0	0%	1	2%
Other method	7	11%	13	19%
Not relevant, as the item was not measured (insignificant)	1	2%	0	0%
Not relevant, as the item was not identified	21	31%	23	34%
Not stated/not clear	9	13%	11	16%
Total	67	100%	67	100%

Costs in the primary sector were typically measured using either a patient-specific or case-costing approach, or another (unspecified) method (e.g. see Box 4.4). In the few cases (n=8) where costs related to home care and/or social care were measured, no dominant approach was observed.

It can be concluded that identification and measurement of costs within the health care sector are often limited to the hospital sector (inpatient and outpatient treatment). The typical approaches used of micro-costing, patient-specific costing and case-costing imply fairly detailed measurement of costs. However, only about half of the HTAs using micro-costing for inpatient or outpatient costs use original data as a primary source (6/13 and 8/13, respectively).

Box 4.4 Economic evaluation of a primary care-based education program for patients with osteoarthritis (OA) of the knee (Lord et al., 1999)
In this HTA by NCCHTA, local general practices were randomized to either an intervention group or a control group. In the intervention group, patients with OA in the knee were invited to participate in four 1-hour group sessions led by a research nurse. The costs to the practices were measured using a patient specific-costing approach, such that:

- Each cost-generating event (e.g. prescribed medications) was registered in the GP case notes
- Each cost-generating event was assessed for its relevance to OA
- Unit costs were estimated for each cost-generating event using published national data

Total costs, for all relevant health care and including the costs of the educational sessions, were estimated for each patient.

Costs to patients and their families, and costs in other sectors

Resource use by patients was identified in 24% (16) of the HTA economic evaluations, and was stated to be irrelevant in one HTA (Table 4.9). Time costs for patients and/or their family (caregiver) were identified in 19% (13) of the HTAs, while these were not relevant in 39% (26) of the HTA economic evaluations. Patient resource use (including time costs) was thus not identified in 82% (55) of the

HTAs, despite the statement in six of these studies that the perspective taken was that of society. In these cases, even if the patient resource use is considered to be insignificant, these costs should be discussed (and identified), and it should be explicitly stated that their value is estimated to be insignificant (zero).

Table 4.9
Identification of patient resource use and other costs in HTA economic evaluations

	Costs for patients		Costs due to productivity loss		Other cost components	
	N	Percent	N	Percent	N	Percent
Identified					25	37%
• Identified for patients	16	24%	11	16%		
• Identified for patients *and* family			2	3%		
Not identified	50	75%	28	42%	42	63%
Not relevant according to the authors	1	1%	26	39%	0	0%
Total	67	100%	67	100%	67	100%

In the HTAs where patient resource use was identified, questionnaires completed by the patients were the primary source of measurement (n=8). 'Other' cost components were identified in 25 economic evaluations – these were typically drug costs related to the hospital sector, primary care or the patients.

Coherence between costs and perspective

It was noted in section 4.1 (see Figure 4.1) that 27% of the HTA economic evaluations were performed from the perspective of the health care sector, while 16% applied a societal perspective (in 47% of HTAs the perspective was not stated). Table 4.10 compares the stated perspective with that implied by the cost components that were identified in the HTA economic evaluations.

Table 4.10
Stated perspective of the HTAs versus actual applied perspective

Stated perspective of the analysis	Applied perspective: Society [1]	Health care sector [2]	Hospital sector [3]	Other [4]	Total
Society	3	1		7	11
Health care sector	1		1	16	18
Hospital/treatment unit				2	2
Third party payer				5	5
Not stated/not clear		3	16	12	31
Total	4	4	17	42	67

[1] A societal perspective identifies costs for inpatient care, outpatient care, physicians and other professional services, home care and/or social care, patients and production loss for patient and/or caregiver, if relevant. It should be noted that, even though resource use is identified, the costs might be estimated to be insignificant (zero).
[2] A health care sector perspective identifies inpatient or outpatient care costs and costs for primary care (physicians and other professional services) or costs for home care/social care.
[3] A hospital sector perspective identifies only inpatient and/or outpatient care costs.
[4] 'Other' applied perspective indicates that some but not all costs components (inpatient and outpatient care, physicians and other professionals, home care and/or social care, patients and production loss for patient and/or caregiver) are identified.

It appears that eight of the eleven HTAs that purported to use a societal viewpoint did not explicitly identify all the relevant cost components. While the reviewers observed that half (33) of the HTA economic evaluations chose costs that were appropriate to the stated study perspective, the appropriateness of the costs was unclear in 48% of the HTAs. In two HTA economic evaluations, the choice of costs was judged to be inappropriate. Such a discrepancy between the chosen (stated) perspective and the actual included costs may give rise to bias, and hence result in incorrect cost-estimates.

Valuation of costs

The identified and measured resources should ideally be valued using their marginal costs. This approach was only used in two of the reviewed HTAs, however, where the marginal costs were estimated as differences in the variable costs between two or more programs. Table 4.11 further illustrates that costs were typically valued using average costs or charges/rates (i.e. the inclusion of fixed costs). In 22% (15) of the HTAs it was not explicitly stated how the costs were valued. The primary sources of cost data were original data or previously published studies. As the table shows, when original data were used, the costs were most frequently valued by average costs, while data from the literature were most frequently valued by charges. While the use of marginal costs is ideal, valuation using average costs can be justified, depending on the time frame of the study – in the long run all costs are variable. Furthermore, valuation using average costs or charges is often more feasible than using marginal costs.

Table 4.11
Source of measurement and valuation of costs in HTA economic evaluations

	Primary method of valuation						
Primary source of measurement	Marginal costs	Average costs	Charges	Other method	Not stated/not clear	Missing	Total
Original data	1	14	4	2	4		25
Studies in the literature	1	5	10		8	1	25
Billings		1	1	1			3
Expert opinion		4	2		1		7
Other source		3	1	1	1		6
Not clear					1		1
Total	2	27	18	4	15	1	67

4.4 Health outcomes

Table 4.12 shows the outcome measures that were applied in the HTA economic evaluations, according to the type of analysis in which they were used. More than one health outcome was used in some HTAs, e.g. both life-years saved and QALYs. In these cases, only one of the outcomes is reported in the table, based on the natural hierarchy described in section 2.4.4. Where cost-minimization analyses stated the measure of outcome, this was included in the appropriate category in Table 4.12 (e.g. process measure).

Of the 23 HTA economic evaluations that used intermediate outcome measures, 15 of these used process measures, such as the number of cases detected/prevented (e.g. the number of hysterectomies avoided in the HTA by MSAC, 1999). In 14 HTAs, effectiveness was measured as life-years gained (or saved) (e.g. the HTA by Ebrahim et al. (1999) on treatment of hypercholesterolaemia, and the HTA by Leivo et al. (1999) on breast cancer screening). In 11 HTAs, outcome was expressed in quality-adjusted life years (QALYs); most of these used both natural units and utilities (e.g. Baladi (1995) assessed the cost-effectiveness of finasteride therapy for the treatment of benign prostatic hyperplasia, see Box 4.5). Few HTAs used QALYs as the only measure of outcome, e.g. the cost-utility analysis of total hip arthroplasty conducted by Givon et al. (1998). The two HTAs that undertook cost-benefit analysis did so alongside a cost-effectiveness analysis and a cost-utility analysis. In the cost-benefit studies, the applied valuation method was either willingness to pay (WTP), as in the HTA by Brown et al. (1996), or human capital, as in the HTA by Evans et al. (1996). In the HTA by Brown et al. (1996), patients were asked WTP questions in order to derive valuations of benefits. An ex-post user-based perspective was used, and the data were collected using a questionnaire with open-ended questions. Box 4.5 provides an example of health outcome measurement in a HTA economic evaluation.

Table 4.12
Outcome measures applied in HTA economic evaluations

Type of analysis	Measure of outcome		N
Cost analysis/cost minimization analysis	None		17
Cost-effectiveness analysis	Intermediate	Surrogate measure	1
		Process measure	15
		Healthy/sick days	4
		Other intermediate	3
	Final	Life-years gained/saved	6
		HRQoL	1
		Saved lives	2
		Other final	5
Cost-utility analysis	QALY		11
Cost-benefit analysis	WTP		1
	Human capital		1
Total			**67**

Note: When more than one measure of outcome in an economic evaluation is used, only one of them is reported in this table using a natural hierarchy: 1) benefit (WTP and human capital), 2) QALY, 3) life-years gained or other final health outcome, 4) intermediate measure.

Box 4.5 Example of health outcome measurement in HTA
Baladi (1995) used cost-effectiveness and cost-utility analysis to assess the use of finasteride in the treatment of benign prostatic hyperplasia (BPH). The treatment was compared to watchful waiting and surgery, and the perspective was that of the health care sector. A decision analytic model was used to assess the costs and health outcomes of the different interventions. The intermediate outcome of BPH treatment is related to urinary flow and volume, e.g. mean urinary flow rate and peak urinary flow rate. But although these measures are indicative of treatment success, they appear to have little significance to patients, who are more likely to value symptom improvement. A symptom score was therefore used as the outcome measure in this study, i.e. HRQoL was used as a final health outcome. For the cost-utility analysis, the magnitudes of the symptom score improvements were used to determine utility values after therapy. The multi-attribute health status classification system HUI II was used to obtain theses utility values. In this approach, the level on each health state attribute is determined and then a score is assigned to each level. All the attribute scores are then combined to obtain utility values. In this study, the utility values were assigned retrospectively.

A generic health status measure was used in only eight evaluations, reported in six HTAs. The dominant measure was the SF-36, which was used in five HTAs. Disease-specific health status measures (i.e. targeted at specific diseases or patient/population subgroups) were used in 11 HTAs.

QALYs were measured in different ways in the cost-utility analyses undertaken as HTA economic evaluations. In three HTAs the measurement of preferences was carried out as part of the study using either time trade-off (1 case) or standard gamble (2 cases) to elicit patients' preference weights. Three HTAs used pre-scored utility instruments - EuroQol (2 cases), QWB (1 case), HUI (1 case), Rosser (1 case), or not stated (1 case). Two of these cases used patient weights of health status, while the source of the weights was not identified in the other three cases. In

three further HTA economic evaluations, the QALY estimates were derived from other studies (e.g. Fitzpatrick et al., 1998), and in one HTA the QALY estimates were obtained by expert judgment (SBU, 1994).

The perspective of the study did not appear to limit the choice of health outcome measure. As Table 4.13 shows, the various health outcomes were used in more or less all the various perspectives.

Table 4.13
Relationship between study perspective and health outcome measure in HTA economic evaluations

	Societal	Health sector	Third party payer	Hospital/ patient	Not stated	Total
Benefit assessment	1	0	0	1	0	**2**
QALY outcome	1	6	0	0	4	**11**
Final health outcome	3	2	2	0	7	**14**
Intermediate and other not final outcome	4	4	2	0	10	**20**
None (CA/CMA)	2	6	1	1	10	**20**
Total	**11**	**18**	**5**	**2**	**31**	**67**

4.5 Discounting

Nearly 70% (46) of the HTA economic evaluations stated the time perspective used for the measurement of costs and outcomes. This is important in assessing whether the time perspective is appropriate for the health technology considered. Ten of the 21 HTAs where the time perspective was not clearly stated were designed as cost or cost-minimization analyses, while the remaining 11 were cost-effectiveness analyses. The majority of these HTAs were retrospective, with data based on previously published studies or expert judgment.

Many of the HTAs without a clear statement of time frame considered technologies that must be expected to have both short and long health consequences, e.g. the prevention of road traffic accidents, the use of regional telemedicine, screening programs for Down's syndrome. An explicit statement of the time frame would thus have been appropriate. In other cases, however, a short-term study perspective is probably sufficient, e.g. in an analysis of post-operative anesthetic procedures for day case surgery, a comparison between fixed and mobile CT and MRI scanners, and vaccination against influenza.

Nearly 70% (46) of the reviewed HTAs did not adjust for different timing of costs and benefits. In one-third of these HTAs, the time frame was short (less than one year) and discounting was thus not relevant. The remaining 21 HTAs discounted costs only or both costs and outcomes (e.g. see Box 4.6). Eight HTAs did not discount outcomes, but gave a justification of why this was not done. Only six of the HTAs that applied discounting included a discussion of the applied discount rate.

Box 4.6 Example of adjusting for different timing in HTA
The study by Leivo et al. (1999) illustrates the handling of different timing of costs and health outcomes. The aim of the study was to evaluate, from a societal perspective, the cost-effectiveness of the Finnish nationwide breast cancer screening program. The time horizon for the study was 31-33 years, and both costs and health outcomes (life-years gained) were discounted to their present value using a discount rate of 3%. The choice of discount rate was discussed in the report, where it was explained that the discount rate in the base case was that recommended by the U.S. Panel on Cost-effectiveness in Health and Medicine. Furthermore, a discount rate of 5% was tested in a sensitivity analysis, being the rate used in previous studies, which would allow comparison of the results with other findings in the literature.

4.6 Presentation of results

Of the 67 HTAs reviewed, 46 (69%) included either cost-effectiveness, cost-utility or cost-benefit analysis (or a combination of the three). In 45 (98%) of these, the primary result was illustrated by a cost-effectiveness ratio or net benefit.

In 14 (32%) of the 44 HTAs that included CEA and/or CUA, the issue of dominance was not discussed (or it was unclear whether it was discussed or not). Furthermore, incremental analysis was absent from approximately one-third of these 44 HTAs (Table 4.14). It should be noted, however, that the calculation of incremental cost-effectiveness ratios (ICERs) is only relevant if non-dominance is present. Box 4.7 illustrates the importance of incremental analysis and consideration of dominance.

Table 4.14
Performance of incremental analysis in HTA economic evaluations

	Cost-effectiveness analysis		Cost-utility analysis		Cost-effectiveness and cost utility analysis	
	N	Percent	N	Percent	N	Percent
Yes	22	67%	1	25%	5	71%
No	10	30%	2	50%	2	29%
Unclear	1	3%	1	25%	-	-
Total	33	100%	4	100%	7	100%

Box 4.7 Example of presentation of results in HTA
In a HTA to assess a program of influenza vaccination in the elderly (DACEHTA, 2000b), the societal costs and health outcomes (life-years gained) were calculated for different organizational models. The results were first presented as *cost-effectiveness ratios* (costs/life-year) for each alternative, where the costs of each organizational model were compared to the costs of *not* offering influenza vaccination. This result is not particularly useful, however, as most elderly receive vaccinations anyway (i.e. there is already an organizational model for vaccination in place). The *incremental cost-effectiveness ratios* were therefore calculated to determine which organizational model gave the best value for money (on the basis that some form of influenza vaccination program should be offered). The results showed that some vaccination models *dominate* the others and should, from an economic perspective, therefore be chosen.

4.7 Sensitivity analysis

There were remarkably few HTAs that dealt with uncertainty in other areas than "data variability", even though it is likely that uncertainty existed in other areas as well (Table 4.15). While 81% of the HTAs used sensitivity analysis to handle uncertainty in data variability, only 1-7% of HTAs handled uncertainty in the areas of generalization, extrapolation or variation in methods.

Table 4.15
Areas of uncertainty handled in HTA economic evaluations

Areas of uncertainty	N	Percent [1]
Data variability	54	81%
Generalization of the results	3	4%
Extrapolating from primary data	1	1%
Variation in the method used	5	7%
None	13	19%

1. Does not sum to 100% as more than one type of sensitivity analysis was used in some HTAs

Box 4.8 illustrates the different areas that can be explored using sensitivity analysis. Since the case of data variability seems rather obvious, examples are only given for the other three areas.

Box 4.8 Examples of types of uncertainty in HTA

An example of uncertainty in *generalization of the results* can be seen in Grieve et al. (1999), where local patient testing for diabetes is compared to conventional hospital-based testing. As the study authors were aware that the number of tests given to patients treated locally was probably higher than in conventional practice, this aspect was tested using sensitivity analysis.

A HTA of influenza vaccination of the elderly (DACEHTA, 2000b) provides an example of uncertainty in *extrapolation from primary data*. In this study, the intermediate measure of effectiveness (number of influenza vaccinations) was extrapolated to a final health outcome (life-years gained). In the base case, it was assumed that the people dying from influenza would have had the same life expectancy as the average person in the age group had they not died of influenza. There is some uncertainty related to this assumption, however. This was handled in a sensitivity analysis, where it was assumed that the people dying from influenza would have had only half the remaining life expectancy of the average person in the age group.

A HTA by Nicholl et al. (1998) evaluated the consequences of additional education to ambulance staff. As the study authors were aware that resource use could be measured in different ways, they compared a top-down method with a bottom-up method using sensitivity analysis, thus testing *uncertainty in the method.*

Table 4.16 summarizes the types of sensitivity analysis that were used to handle uncertainty in the HTAs reviewed (some examples of these are provided in Box 4.9). As expected, simple one-way sensitivity analysis was the most frequently used method, being applied in 73% of the HTAs. It is worth mentioning that in five HTAs, the quite advanced method of probabilistic sensitivity analysis was used. In the 19 HTAs that applied analysis of extremes, six used extreme values that were derived from 95% confidence intervals. No sensitivity analysis was performed in

13 of the HTAs. In one of these, statistical analysis was performed, but otherwise in 18% (12/67) of the HTAs, uncertainty was not handled by either sensitivity analysis or statistical analysis.

Table 4.16
Type of sensitivity analysis in HTA economic evaluations

Types of sensitivity analysis	N	Percent[1]
One-way sensitivity analysis	49	73%
Multi-way sensitivity analysis	9	13%
Threshold analysis	14	21%
Analysis of extremes	19	28%
Probabilistic sensitivity analysis	5	7%
None	13	19%

1. Does not sum to 100% as more than one type of sensitivity analysis was used in some economic evaluations

Box 4.9 Examples of types of sensitivity analyses
A *simple one-way sensitivity analysis* was performed in Pollitt et al. (1997), where a range of discount rates was used. A 6% rate was used in the base case, and this was varied to 0 and 10% to test whether the study results would hold under different assumptions.

In a study by SBU (1996), a reduction in risk and a change in the timing of treatment were tested simultaneously using *multi-way sensitivity analysis*.

Threshold analysis was used by Tasch et al. (1997), where the critical value of the price of antibiotics was investigated in relation to the conclusion of the cost-effectiveness analysis in the base case.

Table 4.17 illustrates the use of statistical analysis in the HTAs reviewed. Of the 20 HTAs that used partial statistical analyses (i.e. either the clinical data or the cost data were stochastic), only six used analysis of extremes. Of the 10 HTAs that handled uncertainty with fully stochastic data, two used bootstrapping while the rest used confidence boxes or presented 95% confidence intervals for both clinical and cost data.

Table 4.17
Statistical analysis applied in HTA economic evaluations

Statistical analysis	N	Percent
Both clinical and cost stochastic data	10	15%
Only clinical stochastic data	20	30%
Only cost stochastic data	0	0%
No statistical analysis	19	28%
Not relevant	10	15%
Not stated / not clear	8	12%
Total	**67**	**100%**

Table 4.18 shows that, in three-quarters (40/54) of the HTAs that performed sensitivity analysis, there was also a discussion of the choice and range of variables included in the analysis.

Table 4.18
Discussion of variables included in sensitivity analysis in HTA economic evaluations

Discussion	N	Percent
Yes	40	60%
No	14	21%
Not relevant, since no sensitivity analysis was performed	13	19%
Total	**67**	**100%**

Further analysis showed that HTAs with prospectively collected data (often stochastic) relied on statistical analysis. HTAs with retrospective data collection (often deterministic data) primarily used sensitivity analysis. HTAs involving CA/CMA appeared less likely to use sensitivity or statistical analysis than other types of economic evaluation; neither did they discuss the handling of uncertainty to the same degree.

4.8 Discussion of results and methodology in the HTAs

All except one of the health technology assessments included a discussion of the study results. Three-quarters of the HTAs also included a discussion of the methodology and methodological limitations, and almost the same number of the HTAs included comparisons with other similar studies.

However, only 43% of the HTA economic evaluations discussed the representativeness of the results for routine practice, while 31% did not (in 26% of the HTAs it was not relevant, as the study was performed within routine clinical practice).

The vast majority (93%) of HTAs did not discuss the issue of equity. Only 4% of the HTAs discussed equity of access to health care, while 3% discussed other equity issues (not relating to health, access to or use of health care).

5 Discussion

Sixty-seven HTAs have been reviewed in this literature survey of economic evaluations undertaken as part of health technology assessment. The discussion of the results in the HTA economic evaluation review is to a large extent based on a comparison to the review of the economic evaluation literature in general. It has not been assessed whether the age structure of the HTAs differ significantly from the age structure of the economic evaluations in general, since this was not possible as the included economic evaluations were not identified in all of the reviews. The age structure of the general economic evaluation *reviews* compared to the HTAs is quite similar, but the reviews probably have included economic evaluations published in the past 20+ years, whereas the HTAs are published from year 1990 and onwards. Therefore the comparisons are made with caution.

It appears that a typical HTA includes two parameters – usually clinical and economic parameters – and is thus a partial health technology assessment (a full HTA would also include patient-related and organizational parameters). Most HTAs assess a treatment, where the intervention is a procedure. The economic evaluation performed usually takes the form of a cost-effectiveness analysis performed from the perspective of the health system, in a comparative analysis with at least one other alternative.

Type of economic evaluation

In order to assess the findings regarding the type of economic evaluation undertaken in HTA, a comparison was made with economic evaluations undertaken in the health care area in general (approximately 40 reviews of approximately 3,000 economic evaluations; see Chapter 3). While cost-effectiveness analysis was performed about as often in HTA economic evaluations (63%) as in general economic evaluations (61%), cost-utility analysis (18%) and cost-minimization/cost analysis (28%) were performed more often, and cost-benefit analysis (3%) less often, than in general economic evaluations (CUA: 10%, CMA: 16%, CBA: 8%). It is encouraging that cost-utility and cost-benefit analyses are actually carried out in health technology assessments. This will to some extent reject the hypothesis that economic evaluations carried out as part of HTAs are more basic than economic evaluations in general.

There appears to be no consensus within formal guideline recommendations regarding the type of economic evaluation that should be performed in the health area. Some countries, e.g. USA (Siegel et al., 1997) recommend the use of cost-utility analysis and sometimes cost-benefit analysis, while other countries, e.g. Australia (Australian Commonwealth Department of Health, 1995) and Canada (Torrance et al., 1996) explicitly state that they do not recommend the use of cost-benefit analysis.

When the chosen type of economic evaluation was linked to the specific type of technology, it was seen that the more sophisticated economic evaluation designs (CUA and CBA) were primarily used in HTAs of pharmaceuticals. This is not surprising, as the pharmaceutical industry in several countries is required to demonstrate the superior cost-benefit of new drugs. No association was found between the design of the economic evaluation and the comprehensiveness of the HTA performed, i.e. a comprehensive HTA (including all four parameters) does not necessarily imply an advanced economic evaluation design (CUA or CBA).

Study perspective

A particular problem noted in the review was that many HTA studies (47%) did not state the perspective from which the economic evaluation was performed (most of these performed CMA/CA or CEA, but four involved CUA). This is of concern, as the choice of perspective defines the types of costs that should be included in the evaluation. It may be that the authors of the HTAs were inexperienced in the performance of economic evaluation (although this is unlikely given the quite sophisticated types of economic evaluation that were performed), or that they were unaware of the recommended reporting formats, or perhaps the perspective of the economic evaluations was determined by the remit of a national HTA agency and was therefore not stated in the report. This is an important issue to clarify, but has not been investigated further here.

For those HTAs where the information was available, there was no clear relationship between the perspective of the study and the type of economic evaluation performed, even though a study from a societal perspective might be expected to use a more advanced design (e.g. CUA or CBA).

Use of the societal and health care sector perspectives was similar among the HTA economic evaluations (16% and 27% respectively) and the general economic evaluations (20% and 25%, respectively). However, considerably more (33%) of the general economic evaluations took a hospital perspective (c.f. 3% of the HTA evaluations). On average, only 6% of the general evaluations did not state the perspective of the study, but this figure varied between 2% and 91% in the individual review studies. Most guidelines recommend the use of a societal perspective, often supplemented with other perspectives that might be relevant for local decision-making (e.g. within a hospital).

Study design

Most (85%) of the HTA economic evaluations were carried out retrospectively with the use of secondary data, most often in the form of a literature review or a meta-analysis. This reflects the general nature of health technology assessment, which is often based on a synthesis of clinical evidence that is gathered from a systematic literature review or a meta-analysis; the economic evaluation is then built upon this review or meta-analysis. A majority (63%) of the HTA economic evaluations were designed as models, where the clinical and cost data were combined in a decision analytical framework.

The method of economic data collections was found to be markedly different in general economic evaluations (see section 3.2), where only 10% of the studies collected economic data retrospectively to clinical data, and modeling was used in 39% of studies. This suggests that an important component of health technology assessment is a synthesis of previously published literature that is then used to make predictions about the future; economic evaluation using primary data (e.g. conducted alongside a clinical trial) is in comparison quite rare in the field of health technology assessment. It is therefore of concern that 21% of the HTA studies used non-systematic reviews as secondary evidence as opposed to systematic reviews and meta-analyses.

Approach to costing

Direct health care costs were identified less frequently in the health technology assessments (inpatient costs: 67%, outpatient costs: 66%, primary care costs: 39%),

than in the general economic evaluations (inpatient costs: 92%, outpatient costs: 85%, primary care costs: 71%). In comparison, costs to patients (24% of HTAs) and time costs (19%) were more frequently reviewed in the HTA evaluations (c.f. 8% and 11%, respectively, in the general economic evaluations).

Guidelines usually recommend that the cost perspective of a study be explicitly stated, that quantities of resources and unit costs be reported separately and that the costs included be appropriate for the stated perspective. In the sample of economic evaluations carried out as part of HTAs, 54%, 51% and 49% adhered to these recommendations, respectively. Relatively few HTA economic evaluations satisfied all the recommendations.

With respect to the sources used for measurement of resource use, HTA economic evaluations used previously published data more often, and billings/charges, expert opinion and 'other' sources less often, than general economic evaluations. Original data were used in just under 40% of both types of evaluations. No formal guidelines exist regarding the sources of resource use, and usually it is simply stated that the sources will vary depending on the type of resource use (e.g. inpatient, outpatient care etc.) being measured. This implies that more than one method can be used within a single economic evaluation, as usually more than one type of resource use is measured.

In general, costs in HTA economic evaluations were valued using average costs or charges/rates, but the valuation method was not clear in 22% of the HTAs.
It appears that costing methodology varies between HTAs, with relatively few HTA economic evaluations meeting the recommendations in guidelines for economic evaluations. It also appears, however, that the costing methodology used in HTA economic evaluation does not differ significantly from that used in economic evaluation in the health area in general.

Health outcomes

The use of intermediate measures is predominant among HTA economic evaluations, despite the lack of established relationships between intermediate measures and final health outcome. It is usually recommended (Anell & Norinder, 2000) to use measures of effectiveness that relate to final health outcome (rather than to output), as this information is more relevant in a decision-making context. The current review suggests, however, that many HTA economic evaluations do not adhere to this recommendation. This may, of course, be related to the timing of the HTA in relation to the lifecycle of the health technology; if the HTA is undertaken early in the lifecycle, the information on final health outcome will probably not exist, and intermediate measures of effectiveness will have to be used instead.

From a theoretical point of view, cost-benefit analysis provides the most complete and relevant information for societal decision-making (Anell & Norinder, 2000) and is well founded in welfare economics. However, this type of analysis is rarely used – this literature review identified only two HTA studies that used the cost-benefit approach – perhaps because it poses considerable methodological and practical problems. It is, of course, encouraging that this type of outcome is used at all, as discussed earlier.

Few of the HTA economic evaluations used QALYs as a measure of health outcome, and it was difficult to identify a preferred methodology. The choice of whose values should guide the valuation of health-related quality of life is depend-

ent on the perspective of the economic evaluation. If a societal perspective is chosen, then the values of the general public should be used. Two HTA evaluations incorporated cost-utility analysis with a societal perspective, but neither used valuations from the general public - one HTA used a pre-scored instrument (Quality of Well-Being), in which the valuations of health status were based on 'expert' opinion, while the other HTA elicited the patients' preferences directly.

The methodology used to measure health outcomes appeared to be similar in HTA evaluations and in health economic evaluations in general. This result should be interpreted with caution, however, as health outcomes were categorized slightly differently in the two reviews. Intermediate measures of effectiveness appeared to be used more frequently in general economic evaluations (53% c.f. 34% in HTA evaluations), but this result is clouded by the inclusion of studies using cost analysis/cost-minimization analysis as a separate category for the HTA economic evaluations.

Use of discounting

Practice differed regarding the use of discounting for future costs and health outcomes, both among the HTA economic evaluations and the general economic evaluations. The HTA economic evaluations included a slightly higher proportion of studies (43%) where no discounting had been performed (*not* including studies where discounting was appropriately not performed) compared to the general economic evaluations (34%); otherwise the patterns were similar for the two types of evaluation. Most guidelines recommend that the time horizon of a study be stated and the long-term effects be incorporated, just as costs and outcomes that occur more than one year in the future should be discounted to their net present value. There is, however, no consensus regarding the choice of discount rate.

Presentation of results

Guidelines for economic evaluation recommend that results be presented in terms of cost-effectiveness ratios or net benefit. These recommendations are followed by most HTA economic evaluation studies. However, among the HTA economic evaluations that included CEA and/or CUA, one-third omitted to discuss dominance and did not perform incremental analysis.

Sensitivity analysis

Guidelines for economic evaluation uniformly recommend that that the robustness of the data used in the economic evaluation be tested using analysis of uncertainty, either as sensitivity analysis or as statistical analysis. Uncertainty was handled in 82% of the HTA economic evaluations with the use of either sensitivity analysis and/or statistical analysis (but 18% of the HTAs did not conduct any form of analysis of uncertainty). While only 52% of the general economic evaluations included analysis of uncertainty, it has become more common to include such analysis. In a recent, extensive literature review undertaken by Briggs & Gray (1999), 83% of the studies that used CEA or CUA also included analysis of uncertainty, a figure which is similar to that of the HTA economic evaluations.

Sensitivity analysis used in HTA economic evaluation was typically simple one-way analysis to test data variability (73%), while simple multi-way analysis, threshold analysis or analysis of extremes, were performed in 13-28% of the HTAs. In the general economic evaluations, simple one-way sensitivity analysis was performed in 61% (although Briggs & Gray (1999) reported a figure of 70% from

their review), while simple multi-way, threshold and analysis of extremes were performed in 5-8% of studies.

A greater difference appeared between the two types of economic evaluation in regard to the use of statistical analysis to investigate uncertainty in stochastic data. Statistical analysis was performed in 45% of the HTA economic evaluations, whereas Briggs & Gray (1999) reported a figure of 5% and Agro et al. (1997) reported the use of partial and full stochastic analysis in 7% and 3%, respectively, of general economic evaluations. This rather large difference may be due to more restrictive criteria being used for statistical analysis in the reviews of general economic evaluations (e.g. HTA economic evaluations that presented results with confidence intervals were classified as performing statistical analysis).

The results of the present review showed that uncertainty in cost data was often handled without any consideration of the underlying statistical distribution. This is similar to the findings from the general economic literature. Briggs & Gray (1999) reported that sensitivity analysis of both resource use and health outcome was often based only on point estimates or expert opinions, with no reference to the actual or presumed underlying variance and distribution of costs and associated confidence intervals.

Discussion of results and methodology

Virtually all the HTA economic evaluations included a discussion of the study results, and most also discussed limitations of the methodology and compared the results with those of other studies. Only 7% of HTAs discussed the issue of equity, however.

Concluding remarks

The aim of this review was to investigate the state of the art of a sample of (67) economic evaluations undertaken as part of health technology assessments. This was then compared to the methodology used in a sample of (approximately 3000) economic evaluations undertaken in the health area in general.

An initial hypothesis was that the methodology used in HTA economic evaluations would not be so well developed as that used in economic evaluations in general. This hypothesis can be rejected, however, as the methodology used in the two types of evaluation was similar in most respects. It should be noted, however, that the HTAs included in this review all stemmed from national HTA agencies, and thus HTAs undertaken in regional centres or at hospital level (which may have been undertaken by less experienced researchers) were excluded if they were not in the agency databases.

An important difference that did appear between the two types of evaluation is in the study design, where the majority of the HTA economic evaluations were conducted retrospectively to the collection of clinical data, with the use of secondary data in the form of a literature review or meta-analysis. These data were often then combined in a decision analytical model. This approach is not seen to the same extent in economic evaluation in general, and is probably due to the nature of a health technology assessment as a synthesis of clinical and other evidence that is gathered from a systematic literature review.

Furthermore, the use of cost-utility analyses was more widespread in the HTA studies than in the general evaluations, and cost-benefit analysis was used in two cases. This indicates the application of advanced methods of economic evaluation in these health technology assessments. With respect to the identification of resource use, patient costs and time costs were more frequently identified in the HTA economic evaluations than in the general economic evaluations. Unfortunately, the perspective of the economic evaluation was not clearly stated in half of the health technology assessments, which is quite a serious flaw.

Despite the existence of several formal guidelines for economic evaluation, the methodology used in evaluation, as well as its quality, appear to vary. Conducting an economic evaluation can be difficult, as suggested by the number of HTA evaluations that did not state the study perspective, did not perform discounting when relevant, did not perform sensitivity analysis and used average costing/charges rather than marginal costing. These are otherwise issues that are of agreed importance for economic evaluations (see Table 2.2).

An important topic not discussed in this report is how important or critical the results of the economic evaluations were for the health technology assessments undertaken. Does an economic evaluation give added value, and does it result in policy recommendations being stronger or even being altered? It was not possible to investigate this issue in the current review, but it should perhaps be considered in future research. We would argue that, since an economic evaluation takes into consideration the opportunity costs of using a given health technology, it will always provide important additional information in a decision-making context.

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Appendix A.
Checklist for the assessment of economic evaluations carried out as part of health technology assessments

Identification

Reference number: _____ (3 digits)

Date of filling in: ____-____-____ (day-month-year)

Reviewer: ___ TC ___ MA ___RJL ___ consensus

Author: _____ (only first author. e.g.: Bernstein, H.P. et al.)

Year of publication: _____ (e.g. 1996)

Year of publication	N	Year of publication	N
1990	5	1996	7
1991	1	1997	9
1993	1	1998	16
1994	3	1999	16
1995	4	2000	5

The title of the HTA report:

_____

The title of published articles, if relevant:

_____

The journal of the published article:

_____

HTA institute:

1	AHCPR/AHRQ	0	ASERNIP-S	19	CCOHTA	0	CVZ
6	DIHTA	5	FINOHTA	0	ITA	2	MSAC
22	NCCHTA	0	NZHTA	11	SBU	0	SMM
0	SFOSS/SWISS-TA	0	VATAP	1	ICTAHC		

Study frame

1. Was the purpose of the study clearly stated?
N

Yes	67
No	0

2. What type of economic evaluation was performed?

Cost-outcome description	2
Cost analysis (CA) or cost-minimization analysis (CMA)	19
Cost-effectiveness analysis (CEA)	42
Cost-utility analysis (CUA)	11
Cost-benefit analysis (CBA)	2
Not clear	0

3. Which parameters were included (besides the economic evaluation)?

Only economic parameters were included	1
Clinical parameters (efficacy, safety, effectiveness, indications etc.)	64
Patient-related parameters (psychological factors, ethics, acceptability, etc.)	18
Organizational parameters (diffusion, centralization/decentralization, use, access, education/training	20

4. Was the type of health care intervention stated?

Screening	10
Treatment	37
Prevention	9
Diagnostic	5
Care-giving	0
Other	6
Not stated/not clear	0

5. Which type of health technology was assessed?

Pharmaceutical	16
Device or equipment	1
Procedure	50
Not stated/not clear	0

6. Was the perspective of the analysis stated?

Society	11
Health care sector	18
Hospital/treatment unit	2
Third party payer	5
Patient	0
Other	0
Not stated/not clear	31

7. Was a comparative analysis performed?

Yes	66
No	1
If yes, state the comparators:	

Study design

8. How was the economic evaluation performed?

Prospective in connection to a clinical study (if yes, go to question 9)	9
Retrospective (if yes, go to question 9 and 10)	57
Neither	1

9. Primary method: What was the source of the clinical evidence?

RCT	7
Other primary study	13
No primary method was used as clinical evidence	47

10. Secondary method: What was the source of the clinical evidence?
(Does not sum to 67 reports since some HTAs used more than one method)

Meta-analysis of RCTs	8
Meta-analysis of non-RCTs	1
Systematic review	11
Unsystematic review	14
Expert panel	4
Public files	1
Other	1
No secondary method was used as clinical evidence	19
Not clear	1

11. Was it stated that the optimal sample size was calculated?

Only for the clinical study	2
Only for the economic evaluation	0
Was calculated for both the clinical and the economic study	0
No, but the sample size was stated	20
No, neither calculated nor stated	2
Not relevant, since it wasn't a sample	41
Not stated/not clear	2

12. What type of modeling was used?

Markov model	4
Decision tree	31
Other	7
Modeling was not used	23
Not stated/not clear	2

Costs

Identification of resource use:

13. Were quantities of resources reported separately from their unit costs?

Yes, in all cases	34
Yes, in some cases	15
No	18

14. Was inpatient care identified?

Yes	45
No	21
Not relevant according to the authors of the study	1

15. Was outpatient care identified?

Yes	44
No	23
Not relevant according to the authors of the study	0

16. Were physician and other professional services in the primary health care sector identified?

Yes	26
No	40
Not clear	1
Not relevant according to the authors of the study	0

17. Was home care and/or social care resource use identified?

Yes	8
No	59
Not relevant according to the authors of the study	0

18. Was resource use by the patient identified?

Yes	16
No	50
Not relevant according to the authors of the study	1

19. Was production loss for patient and/or caregiver identified?

For the patient	11
For the caregiver	0
For both patient and caregiver	2
No, not relevant according to perspective/the authors of the study	26
No	28

20. Were other cost components identified?

Yes:	25
No	42

21. Was the choice of costs appropriate in relation to the study perspective?

Yes	33
No	2
Not clear	32

Measurement of resource use:

22. What was the primary source(s) of the measurement of resource use?

Original data	25
Studies in the literature	25
Billings	3
Expert opinion	7
Other: _____	6
Not clear	1

23. How was inpatient care measured?
(Does not sum to 67 reports since some HTAs used more than one method)

Micro-costing	13
Patient-specific costing or case-costing (tracking individual patients)	9
Costs per weighted case or costs per weighted day (e.g. DRG)	4
Specialty per diem (daily rates for specific hospital departments)	3
Generic per diem (daily rates set at national, regional or hospital level)	1
Other method: _____	7
Not relevant, since the item was not measured due to its insignificance according to the authors of the study	19
Not relevant, since the item was not identified	1
Not stated/not clear	0

24. How was outpatient care measured?
(Does not sum to 67 reports since some HTAs used more than one method)

Micro-costing	14
Patient-specific costing or case-costing (tracking individual patients)	4
Costs per weighted case or costs per weighted day (e.g. DRG)	1
Specialty per diem (daily rates for specific hospital departments)	1
Generic per diem (daily rates set at national, regional or hospital level)	1
Other method: _____	14
Not relevant, since the item was not measured due to its insignificance according to the authors of the study	0
Not relevant, since the item was not identified	23
Not stated/not clear	11

25. How were physician and other professional services measured?
(Does not sum to 67 reports since some HTAs used more than one method)

Micro-costing	3
Patient-specific costing or case-costing (tracking individual patients)	7
On an hourly basis	3
Cost per encounter	1
Other method: _____	8
Not relevant, since the item was not measured due to its insignificance according to the authors of the study	0
Not relevant, since the item was not identified	42
Not stated/not clear	4

26. How were home care and/or social care measured?

Micro-costing	1
On an hourly basis	1
Cost per encounter	0
Other method: _____	5
Not relevant, since the item was not measured due to its insignificance according to the authors of the study	1
Not relevant, since the item was not identified	59
Not stated/not clear	0

27. How were patient costs measured?

Questionnaire completed by the patients	8
Patient diary	1
Other method: _____	6
Not relevant, since the item was not measured due to its insignificance according to the authors of the study	3
Not relevant, since the item was not identified	47
Not stated/not clear	2

28. How was production loss measured?

Human capital approach	7
Friction cost approach	0
Not relevant, since the item was not measured due to its insignificance according to the authors of the study	4
Not relevant, since the item was not identified	51
Not stated/not clear	3

29. How were other costs measured?

Write: _____

Valuation of costs:

30. How were the costs primarily valued?

Marginal costs	2
Average costs	27
Charges	18
Other method: _____	4
Were not valued	1
Not stated/not clear	15

31. How was production loss valued?

Average wage rates	5
Average wage rates corrected for age and sex	1
Other method: _____	1
Not relevant	55
Was not valued	1
Not stated/not clear	4

Consequences (effectiveness)

For cost-effectiveness analysis:

32. What was the measure of effect?

Intermediate measure of effect	32
Final measure of effect	21

33. Was a generic health status profile used?

No	61
SF-36	5
Nottingham Health Profile	0
Sickness Impact Profile	0
Other: _____	3
Not relevant	0

34. Was a disease-specific health status profile used?

No	56
Yes: _____	11
Not relevant	0

For cost-utility analysis:

35. Was the type of quality of life measurement stated?

QALYs gained, where the measurement of preferences was part of the study	2
QALYs gained, where a pre-scored, health status classification system was used	3
QALYs gained, where results from other studies were used as estimates	3
QALYs gained, where the results were assumed	1
Both measurement as part of the study and use of pre-scored system	1
Other method	1
Not stated/not clear	1

36. Was the method for obtaining preference weights stated?

Rating scale	2
Time trade-off	1
Standard gamble	2
Person trade-off	0
Other: _____	0
Not relevant (if pre-scored)	8
Not stated	0

37. Whose preferences were used in the valuation?

Patients	3
Professional bodies/interest groups	0
Informal caregivers	0
Health professionals	0
The society	0
Other: _____	0
Not relevant (if pre-scored)	8
Not stated	0

38. What pre-scored, multi-attribute health status classification system was used?

EuroQol	2
QWB	1
HUI	1
15D	0
Rosser	0
Other: _____	0
Not relevant (if direct measurement of preferences)	6
Not stated	1

39. Which group identified health status in the pre-scored health status classification system?

Patients	2
General public	0
Other: _____	3
Not relevant (if direct measurement of preferences)	6
Not stated	0

For cost-benefit analysis:

40. Which person-group was asked WTP questions?

Currently diseased	1
Currently non-diseased, at future risk	0
The general population	0
Not stated/not clear	0

41. Which type of benefit was measured?

Patient value	1
Option value	0
Altruistic value	0
Not stated/not clear	0

42. What was the perspective of valuation?

Ex-post user-based perspective (WTP for consumption)	1
Ex-ante insurance-based perspective (WTP for having the program available)	0
Ex-ante tax-based perspective (WTP for having the program available for all)	0
Not stated/not clear	0

43. By which approach was the benefit measured?

Human capital	1
Hedonic pricing	0
Travel cost	0
Willingness to pay	1
Not stated/not clear	0

44. How were the data collected?

Survey/questionnaire	1
Interview	0
Other: _____	1
Not stated/not clear	0

45. What valuation elicitation method was used?

Open-ended questions	1
Bidding game	0
Payment cards	0
Take it or leave it	0
Take it or leave it with follow-up	0
Not stated/not clear	0

Adjustment of costs and consequences for differential timing:

46. Was the time horizon for the costs and consequences stated?

Yes	46
No	21
Time horizon: _____	

47. Were both costs and consequences discounted?

Both costs and consequences were discounted	13
Only costs were discounted	8
Only consequences were discounted	0
Not relevant (if the time horizon is short)	17
No	29
Not stated/not clear	0

48. Was an explanation given, if costs and/or consequences were not discounted?

Yes	8
No	35
Not relevant (if they were discounted)	24

49. Was there a discussion of the discount rate applied?

Yes	6
No	17
Not relevant	44

Presentation of the results:

50. Were the major outcomes presented in the form of a ratio or net-economic benefit?

Yes: _____	45
No	22

51. Was there a discussion of dominance?

Yes	41
No	23
Not clear	3

52. Was an incremental analysis of costs and consequences performed?

Yes	31
Only an incremental analysis of costs	13
Only an incremental analysis of consequences	0
No	21
Not clear	2

Sensitivity analysis:

53. What areas were analyzed in a sensitivity analysis?
(Does not sum to 67 reports since some HTAs used more than one method)

Data variability	54
Generalization of the results	3
Extrapolating from primary data	1
Variation in the used method	5
Other: _____	0
None	13
Not stated/not clear	0

54. Which types of sensitivity analysis were performed?
(Does not sum to 67 reports since some HTAs used more than one method)

One-way sensitivity analysis	49
Multi-way sensitivity analysis	9
Threshold analysis	14
Analysis of extremes	19
Probabilistic sensitivity analysis	5
Other: _____	0
None	13

55. If data on costs or consequences were stochastic, was appropriate statistical analysis performed?

Both with clinical and cost stochastic data	10
Only with clinical stochastic data	20
Only with cost stochastic data	0
No	19
Not relevant	10
Not stated/not clear	8

56. Was the choice of variables and their range for the sensitivity analysis discussed?

Yes	40
No	14
Not relevant, since no sensitivity analysis was performed	13

Discussion:

57. Was there a discussion of the study results?

Yes	66
No	1

58. Were the results and the applied methodology and methodological limitations discussed?

Yes	51
No	16

59. Were the results and the methodology compared with those of others who have investigated the same question?

Yes	48
No	19

60. What type of equity was discussed?

Equity was not discussed	62
Equality of access	3
Equality of use	0
Equality of health	0
Other type of equity	2

61. Did the study state whether the results were representative of routine practice?

Yes	29
No	21
Not relevant, since the study was performed under routine practice	17

General impression:

62. What was the general impression of the study?

Good	NA
Average	NA
Bad	NA

63. How was the reporting of the study?

Good	NA
Average	NA
Bad	NA

Appendix B.
List of HTA-agencies

Below are listed the national agencies of technology assessment, who have an INAHTA membership. These were initially included in the review.

AETS	Agencia de Evaluación de Tecnologias Sanitarias (Spain)
AHRQ (formerly AHCPR)	Agency for Healthcare Research and Quality (USA)
ANAES	L'Agence Nationale d'Accréditation et d'Evaluation en Santé (France)
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical
CCOHTA	Canadian Coordinating Office for Health Technology Assessment (Canada)
CVZ	College voor Zorgverzekeringen/Health Care Insurance Board (The Netherlands)
DIHTA	Danish Institute for Health Technology Assessment (Denmark)
DIMDI	German Institute for Medical Documentation and Information
ETESA	Unidad De Tecnologias De Salud (Chile)
FINOHTA	Finnish Office for Health Care Technology Assessment (Finland)
ICTAHC	Israel Center for Technology Assessment in Health Care (Israel)
INHEM	Instituto Nacional de Higiene Epidemiologia y Microbiologia (Cuba)
ITA	HTA Unit of the Institute of Technology Assessment (Austria)
MSAC	Medical Services Advisatory Committee (Australia)
NCCHTA	National Coordinating Centre for Health Technology Assessment (UK)
NZHTA	New Zealand Health Technology Assessment (New Zealand)
SBU	Swedish Council on Technology Assessment in Health Care (Sweden)
SMM	The Norwegian Centre for Health Technology Assessment (Norway)
SWISS/TA	Swiss Science Council/Technology Assessment (Switzerland)
VATAP	Veterans Affairs Technology Assessment Program (USA)

Appendix C.
HTA reports included in the review

Anderson DR, O'Brien B, Nagpal S et al. Economic evaluation comparing low molecular weight heparin with other modalities for the prevention of deep vein thrombosis and pulmonary embolism following total hip or knee arthroplasty. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1998.

Baladi J-F. Cost-effectiveness and cost-utility analysis of finasteride therapy for the treatment of benigh prostatic hyperplasia. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1995.

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Canadian Coordinating Office for Health Technology Assessment. Leukoreduction: the techniques used, their effectiveness and costs. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1998.

Canadian Coordinating Office for Health Technology Assessment. Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part II. The cost-effectiveness of SSRIs in treatment of depression. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1997.

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Danish Institute for Health Technology Assessment. Influenza vaccination of the elderly. DIHTA, 2000.

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Ilersich AL. The cost-effectiveness of G-CSF for prophylaxis of febrile neutropenia after standard dose chemotherapy. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1997

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Kauppinen R, Sintonen H, Vilkka V, Tukiainen H. Long-term (3-year) economic evaluation of intensive patient education for self-management during the fist year in new asthmatics. *Respiratory Medicine* 1999; 93: 283-89. FINOHTA

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McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review. *Health Technology Assessment* 1998; 2(12). NCCHTA

Medicare Services Advisory Committee. Saline infusion sonohysterography. MSAC application 1007, 1999.

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Appendix D.
Search strategy for review in Chapter 3

In order to find previously published literature reviews of economic evaluations of health technologies, a literature search was conducted in OVID, where Medline, Embase and Cinahl were searched. A HealthStar search was also conducted in the NLM's Internet Grateful Med search engine. The search results are shown in the table below.

#	Search History	Medline 1966 to Dec. Week 4 2000	Embase 1980 to 2000 Week 52	Cinahl 1982 to Dec. 2000	HealthStar 1975 – Dec. 2000[1]
1	Cost-benefit Analysis/ or 'economic evaluation'.mp or "Costs and Cost Analysis"/ or Economics, Medical/ or Economics, Hospital/	51006	28929	4327	9820[2]
2	review.mp	218009	524270	17471	Defined as review
3	checklist.mp	4021	3676	2038	2352
4	*Guideline Adherence/st	30	0	0	1406
5	'methodological standards'.mp	68	71	4	187
6	adherence.mp	17957	20876	1063	4914
7	*score/	0	0	0	-
8	literature.ti	35372	21594	2362	
9	"*journal".ti	3488	14102	2312	
10	"*article".ti	6197	1546	4259	
11	"*publication".ti	1441	815	428	
12	8 or 9 or 10 or 11	46158	37911	9077	6396
13	3 or 4 or 5 or 6	22040	24589	3078	-
14	*1 and 2 and 12 and 13*	*6*	*6*	*1*	-
15	*1 and 3*	*27*	*44*	*13*	*15*
16	*1 and 4*	*0*	-	-	*9*
17	*1 and 5*	*10*	*13*	*1*	*6*
18	*1 and 6*	*94*	*77*	*11*	*15*
19	*1 and 12*	*210*	*135*	*97*	*16*
	Included articles (counting overlap between the databases)	17	16	3	4
	Included articles (not counting overlap between the databases)	**17**	**4**	**1**	**2**

Notes:
1. Excluding Medline overlap
2. Query in HealthStar: Costs and Cost Analysis/ or Cost-Benefit Analysis/ or Health Care Costs/ or *cost or Economics, Hospital/ or Economics, Medical

Within OVID, a search strategy was first built and employed in Medline alone. Afterwards the same strategy was applied to the Embase and Cinahl databases. In the table, the searches 14 - 19 (italicized) were the 'final' search results (806 articles in total). It should be noted that these searches were overlapping, i.e. an article may be identified in both search number 14 and in search number 16. For each article, the titles and abstracts were read in order to include articles relevant to the literature review. To be included, an article had to satisfy two general criteria. First, the article should include some sort of checklist concerning the methodological

principles in economic evaluations, and secondly, this checklist must have been applied to economic evaluations of health technologies in a literature review focusing upon the methods used.

This reading of abstracts resulted in the inclusion of 24 articles, of which 17 articles were discovered by the Medline search. The searches in Embase and Cinahl revealed an additional 4 and 1 article, respectively, which were not included in the Medline search. Finally, the HealthStar search resulted in yet another 2 articles. Besides the systematic search in these databases, other relevant articles were identified that were already in the hands of the present authors or were identified through the reference list of some of the other literature reviews. This search provided an additional 16 articles for the literature review.

In total, the systematic search and the articles identified by other means resulted in the identification of 57 articles that, according to the abstracts, presented literature reviews of economic evaluations of health technologies. However, 17 of the 57 articles were excluded after reading of the full article, as they did not fulfill the criteria for inclusion (either they only presented a checklist or focused on the results of a health technology).

The final sample of literature reviews of economic evaluation methods included in Chapter 3 consisted, therefore, of 40 articles in total.